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Snake Venoms. I. Their Constitution and Therapeutic Applications. CHARLES H. KELLAWAY, M.C., M.D., M.S. (Melb.), F.R.C.P. (Lond.) 1

Snake Venoms. II. Their Peripheral Action. CHARLES H. KELLAWAY, M.C., M.D., M.S. (Melb.), F.R.C.P. (Lond.) 18

A Puzzling Case of Obstipation Apparently Due to Mesenteric Adenitis. I. RIDGEWAY TRIMBLE, M.D. 40

Experimental Study of Congenital Syphilis, Including a Study of the Infectiousness of Blood, Uterus and Placenta of Pregnant Rabbits with Early Syphilis. JAROLD E. KEMP, M.D., AND PAUL D. ROSAHN, M.D. 45

Book Reviews 56

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SNAKE VENOMS

I. Their Constitution and Therapeutic Applications[1]

CHARLES H. KELLAWAY, M.C., M.D., M.S. (Melb.), F.R.C.P. (Lond.)

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Snake venoms are beautifully adapted to their functions in the reptilian economy. They serve rapidly to immobilise living and active prey which is to be swallowed whole. To assist in the digestion of this unmasticated food, the venom must be distributed throughout the body of the victim while it is yet alive. These ends can only be achieved by the injection of the venom, and the venomous snakes are provided with a biting mechanism which in its most perfect form anticipated the discovery of the hypodermic syringe.

The venom apparatus consists of a gland, the duct from which leads to the base of a needle-sharp fang which is either grooved along its anterior border as in the *Colubridae*, or canaliculated as in the *Viperidae*. The gland, which is homologous with the mammalian salivary parotid, is situated superficially behind the orbit. It is a pear-shaped structure with a dense fibrous-tissue capsule into which the anterior temporal muscle is inserted. Contraction of this muscle during the act of biting exerts torsion upon the gland and expresses some of its secretion. The duct leads forward and opens by a papilla in the anterior wall of the *Vagina dentis*, a fold of mucous membrane which firmly embraces the base of the fang and, by approximating the papilla of the duct to the upper opening of the canal in the fang or to the upper part of the groove, provides for the transport of the venom along this channel.

[1] Lecture I, of the twelfth course of lectures under The Charles E. Dohme Memorial Lectureship of The Johns Hopkins University School of Medicine. Delivered November 5, 1936. Lecture II, *The Peripheral Action of Snake Venoms*, appears in this same number of the *Bulletin*; Lecture III, *Snake Venoms and Immunity*, will appear in a subsequent issue.

The most efficient biting apparatus is found among the *Viperidae*. This family includes most of the dangerous venomous snakes of the New World as well as many of those of Europe, Asia and Africa. In these species the head is broad, the venom glands large, the fangs are long and canaliculated and are erected when the mouth is opened to strike. This movement of striking is carried out with great speed and force and the fangs are plunged deeply into the body of the victim.

The Colubridae embrace the remainder of the venomous species. They are widely distributed over most of the globe and include also the venomous sea snakes. They present three varieties of biting mechanism. The *Aglyphous* series have solid teeth which are not grooved; the *Opisthoglyphous* series have grooved posterior maxillary teeth, and the *Proteroglyphous* series, which include nearly all the dangerous venomous snakes of this family, are provided with grooved anterior maxillary teeth.

The osteological transitions through these species of serpents to the more highly specialised vipers have been described by Phisalix (1922). The skull and superior maxillae are shortened and the quadrate bones are progressively lengthened. Fairley (1929) has shown that in the Australian species these changes are associated with an increasing degree of capacity for forward rotation of the fangs, reaching its greatest extent in the death adder, *Acanthophis antarcticus*, which thus exhibits transition towards the development in the *Viperidae* of the ability to erect the fangs by rotation of the maxillae upon their transverse axis of articulation with the prefrontals.

In these colubrid snakes with short grooved fangs some compensation for the relative inefficiency of their biting mechanism, compared with that of the vipers, is afforded by the more deadly character of their venoms. It is noteworthy that two of the most potent of snake venoms are those of the Australian tiger snake (*Notechis scutatus*) and a sea snake with a very poorly developed biting apparatus (*Enhydrina schistosa*).

Venom is a mixed saliva composed of the secretion of the serous venom glands together with that of certain supra-labial mucous glands which pour their secretion into the duct. It is collected, free from admixture with the secretion of other glands in the mouth, by making the snake bite through a piece of rubber-dam or waterproof

cloth stretched over the mouth of a glass vessel. The fangs pass through this covering material and the venom alone is collected. To obtain a maximum yield the venom glands are gently massaged while the snake is biting and for a few moments afterwards.

The venom, as collected, is a clear liquid of very varying viscosity. It may be colourless, straw-coloured or bright yellow. It contains a little cellular debris and occasionally is even turbid from this cause. The proportion of solids is so variable that fresh venom should never be used for quantitative work. Martin and Smith (1892), for example, found variations in the solid content of the venom of the black snake (*Pseudechis porphyriacus*) from 12 to 67 per cent, and Fairley and Splatt (1929) in that of the death adder (*Acanthophis antarcticus*) from 19.5 to 42 per cent.

When dried, venoms form whitish or yellowish pseudocrystalline scales which must be powdered and redried over sulphuric acid *in vacuo* to ensure the removal of included water. If thoroughly dried and sealed in glass, they retain their activity for many years.

Apart from water, venoms contain variable amounts of pigment, small amounts of ether-soluble substances, salts (chiefly chlorides and phosphates), proteins coagulable by heat, proteoses and sometimes peptones. Some of their activities are due to enzymes and it is not known whether their toxicity is due to the presence of minute amounts of highly active substances adsorbed to known constituents of this complex mixture or to these protein constituents themselves.

Before discussing some of the attempts which have been made to fractionate snake venoms I shall indicate the variety of toxic activities which they manifest. These vary both qualitatively and quantitatively over the wide range of venoms which have been investigated.

Many snake venoms present a dominantly toxic action which determines the nature of the symptoms observed and the mode of death following the bite.

A large group of venoms, chiefly those of the proteroglyphous *Colubridae* of which the venoms of the Indian cobra (*Naia naia*), of *Enhydrina schistosa* and of the Australian death adder are typical, are strongly curarizing in action. The symptoms presented in poisoning are in part due to loss of tone and paralysis of the skeletal muscles, and death may take place from paralysis of the muscles of respiration

with slowly or rapidly developing asphyxia. The picture is, however, complicated by the activity next to be described.

Another group of venoms chiefly those of the *Viperidae* and typified by the venoms of the genus *Bothrops* and *Crotalus* (not including that of *Crotalus terrificus* which is said to be truly "neurotoxic") cause death by peripheral circulatory failure. These two toxic activities of snake venoms will be considered in detail in my second lecture.

THE COAGULANT AND ANTI-COAGULANT PROPERTIES OF SNAKE VENOMS

A third cause of death is due to the presence of thrombins or kinases in venom which, when injected intravascularly, cause coagulation of the blood. This is happily rare, but may occur with the venoms of the Daboia, *Vipera russellii*, with some venoms of the genus *Bothrops* and with that of the Australian tiger snakes when the fangs directly penetrate into a vessel. Following the bite of some Australian brown snakes of the genus *Demansia*, death from intra-vascular coagulation may occur without fortuitous injection into the bloodstream by the fangs.

In vivo the most actively coagulant venoms are those of the Australian snakes of the genera *Pseudechis* and *Notechis* and of the Indian viper *Echis carinata*.

A less powerful coagulant activity is manifested by the venom of the Daboia, *Vipera russellii*. The venoms of many South and Central American snakes of the genus *Bothrops* are strongly coagulant (Noc (1904), Houssay and Sordelli (1919), Brazil and Vellard (1928)), as is also that of *Crotalus terrificus*, the tropical rattlesnake. These venoms when injected intravenously in appropriate dosage cause intravascular coagulation, but in minute dosage, or when very slowly injected, render the blood incoagulable by converting all the available fibrinogen to fibrin, which is deposited throughout the vascular system on the red blood cells and on the lining endothelium, particularly in the portal vessels (Mellanby (1909), Houssay and Sordelli (1919)). Mellanby has shown that the venom of *Notechis scutatus* contains a kinase because its coagulant action on bird and mammalian plasma rapidly increases within the first few moments after admixture with plasma as a result of the formation of additional thrombin.

Other venoms possess anti-coagulant properties, both when injected intravenously and also *in vitro*, notably the venoms of the Indian cobra *Naia naia*, the hamadryad *Naia hannah*, the water moccasin *Agkistrodon piscivorus*, the Australian copperhead *Denisonia superba* and the death adder *Acanthophis antarcticus*. The venom of the cobra *in vivo* is said to act in this way in a two-fold manner, by the presence of an anti-kinase in the venom and by the formation of an anti-thrombin. According to Houssay and Sordelli (1919), no appreciable amount of anti-thrombin is formed, and coagulation is inhibited both *in vitro* and *in vivo* owing to the destruction of thrombokinase. The anti-coagulant activity of *Crotalus adamanteus*, *in vitro*, is due to proteolysis of fibrinogen.

HEMOLYSIS BY SNAKE VENOM

A large number of snake venoms exert a destructive action upon red blood corpuscles both *in vivo* and also *in vitro*. They vary qualitatively as well as quantitatively in respect of this activity. Some venoms are capable of haemolysing thoroughly washed red blood cells, but others require the presence of an activator. Among the former are the venoms of the Indian cobra (*Naia naia*) and of the Australian black snake and copperhead, and among the latter the Crotaline venoms. For these last, homologous serum contains an activator, (Flexner and Noguchi (1902)), while the former group are actually inhibited by serum and by other proteins (Kyes (1902/1910), Kellaway and Williams (1933), Holden (1934)). Some venoms though very highly toxic have, like that of the Australian tiger snake, only slight action on red blood cells.

The erythrocytes of mammalian species vary greatly in their susceptibility to snake venom haemolysis and the order of their susceptibility roughly coincides with that to haemolysis by hypotonic saline and with their resistance to saponin haemolysis (Rhyvosh, 1907). The red blood cells of the sheep and ox, for example, are highly resistant and those of the guinea-pig and dog are highly susceptible to haemolytic venoms. Haemolysis by snake venom is preceded by swelling of the corpuscles.

Not only do venoms vary in respect of their ability to haemolyse washed cells with and without activators, but the washed erythro-

cytes of different species also exhibit different behaviour, in the presence and absence of serum, with one and the same venom. For example, the haemolysis of the thoroughly washed red blood corpuscles of the horse and dog by cobra venom is accelerated, and that of human, cat and rabbit cells is inhibited by homologous serum.

Snake-venom haemolysis is even more complicated than the facts already detailed would suggest. Some haemolytic venoms when present in excess actually inhibit haemolysis. Noguchi (1905) showed that this inhibitory property in the case of cobra venom was destroyed by heating to 100°C. for five minutes, though the haemolytic power of the venom still remained. Cells treated with excess of venom were rendered resistant also to haemolysis by hypotonic saline or by saponin.

Our knowledge of the mechanism of haemolysis by snake venoms is still very incomplete. The researches of Kyes (1902–1910) and of many others who worked in this field, notably those of Delezenne and his colleagues (1911–1914), led to the recognition that haemolysis may occur by the formation of chemical lysins by the action of phosphatidases in the venoms. In the case of some venoms there is evidence of a more directly haemolytic action.

Haemolysis of snake venoms is powerfully influenced by the hydrogen-ion concentration (Bang (1908–10), Holden (1934)). *In vivo* and in systems heavily buffered with serum *in vitro* this influence is not so important, but much of the work on haemolysis of washed corpuscles is of little value, because the hydrogen-ion concentration has not been adequately controlled. Studies of the effect of change in pH have indicated further possibilities concerning the complexity of the haemolytic action of Australian venoms.

Holden (1934–1935) studied the haemolysis of rabbit cells by the venom of the Australian copperhead, using the methods developed by Ponder (1921). Isotonic salt solution, buffered with sodium acetate and adjusted to the required pH with acetic acid, was used both for washing and suspending the cells. It was found that variation in hydrogen-ion concentration not only altered the times of haemolysis but modified the form of the time-concentration curves. The results suggest that this venom and that of the Australian black snake, which behaves like it, contain two active agents—one which has a direct

action on the red blood cells and is most effective at pH 6, and another corresponding to the "phosphatidase" of other venoms, which acts by the formation of a powerful chemical lysin and is most effective at pH 7.7.

The first haemolysin is greatly diminished in activity at pH 7.7. It haemolyses the cells of the rabbit and guinea pig, but not those of the ox or sheep. It at once dissolves the stroma of susceptible cells which have been laked by water but not that of resistant cells. Its action is accelerated by small amounts of calcium chloride and by lipoids of haemolysable cells. It is not accelerated by lecithin at pH 6. It is inhibited by excess of venom, by some proteins, for example, serum albumin, and by the lipoids of resistant cells. Its latent period is abolished by calcium chloride.

The second active agent in the presence of lecithin haemolyses all species of red corpuscles and dissolves the stroma of cells resistant to venom alone. Proteins and extracts of the lipoids of resistant cells have only slight inhibitory action upon it. It is not inhibited by excess of venom. It is less resistant to thermal inactivation than the direct haemolysin.

Time-concentration curves at pH 5.6–pH 6, plotted logarithmically, show an almost strict proportional relation between time and concentration—the logarithms of the concentrations being proportional to the reciprocal of the logarithms of the times. This appears to be characteristic of haemolysis of the direct type.

At more alkaline pH values (8.0, 7.2 and 6.6) the rate of haemolysis was slowed, and at high and low concentrations of venom the curves tended to be flattened with respect to the axis of concentration. In these regions the time of haemolysis is but little affected by increasing concentrations of venom. This is characteristic of haemolysis by chemical lysins.

Holden's observations in regard to the effects of the suspensions of lipoids of the stroma of various species of erythrocytes in inhibiting or accelerating direct haemolysis are of interest from the standpoint of the varying susceptibility of different species to haemolysis *in vitro*. Lipoids of rabbit and horse erythrocytes, which are susceptible, accelerate, and those of sheep cells, which are resistant to haemolysis, inhibit.

Holden also studied the inhibition of haemolysis by proteins. Serum proteins are by far the most active in this respect. This inhibition must be a factor in preventing the occurrence of direct haemolysis *in vivo*.

$Ca^{\cdot\cdot}$ has a profound influence upon snake-venom haemolysis. Holden found that at all hydrogen-ion concentrations it diminished the latent period in velocity curves. Its presence is said to be necessary for the formation of "lysocithine" and for the destruction of this chemical lysin by excess of venom.

In animals poisoned by copperhead venom, haemolysis occurs in the sheep, whose erythrocytes are highly resistant *in vitro* except in the presence of lecithin. It also occurs in the horse and rabbit, but rarely in the guinea-pig, whose erythrocytes are susceptible *in vitro*.

The occurrence of haemolysis in the sheep makes it probable that in this animal lysocithine formed by action on lecithin in the plasma is the effective agent.

THE CYTOLYTIC ACTION OF VENOMS—HAEMORRHAGIN

One of the most striking features of poisoning by viperine venoms is the intense haemorrhagic oedema caused by them at the site of injection, together with multiple haemorrhagic lesions in the serous membranes, lungs and other viscera. Some of the venoms of the family *Colubridae* have a similar but less intense action. Among the venoms of the Australian species those belonging to the genus *Pseudechis* cause the most intense local and general haemorrhagic effects. For example, the subcutaneous injection of a lethal dose of the venom of *Pseudechis guttatus* in the guinea-pig causes haemorrhagic oedema spreading over the whole ventral surface of the animal. There is an intense haemorrhagic oedema of the lungs, together with haemorrhagic pleural effusion and ascites. Finally, the adrenal medulla is disrupted by haemorrhage, being as severely affected by this venom as it is by diptheria toxin.

Mitchell and Reichert (1886) demonstrated for *Crotalus* venom, and Martin (1895) for that of the Australian black snake, that these haemorrhagic effects were associated with the presence in the venom of proteins coagulable by heat and were due to injury to the endothelial lining of capillaries and small veins. Flexner and Noguchi (1902b)

showed that the degree of toxicity of crotaline venoms could be related to their richness in "haemorrhagin," which they regarded as a cytolysin for vascular endothelium. Crotaline venom can be deprived of its haemorrhagic power by heating to 75°C. for 30 minutes (Flexner and Noguchi), or by treatment with weak hydrochloric acid (Morgenroth, 1906). This property of the viperine venoms is associated with their capacity to cause a profound fall of blood pressure when injected intravenously—a phenomenon which will be analysed in our next lecture.

Cytolytic action upon vascular endothelium is only one manifestation of the destruction of tissue cells by snake venoms. Venoms, particularly those of the *Viperidae* cause fatty degeneration and necrosis in the parenchyma of various organs—notably in the liver and kidneys and in skeletal muscle. Flexner and Noguchi (1905) believed, on the evidence of adsorption experiments, that venoms contained several cytolysins, specific for various cells, testis, liver and kidney, and distinct from the haemolytic property of the venom.

THE FERMENT ACTIONS OF SNAKE VENOMS

Since venom is a highly specialised saliva it might be anticipated that some of its activities would be due to ferments, and in fact, in 1881, de Lacerda showed that the venom of a species of *Bothrops* emulsified fat, coagulated milk, dissolved fibrin and coagulated egg-white, though it had no diastatic action upon starch.

In Houssay's laboratory, the early observations of de Lacerda have been extended by the study of many venoms. Houssay and Negrete (1918), in confirmation of Flexner and Noguchi (1902b) and of Noc (1904), have shown that snake venoms possess proteolytic action on fibrin, casein and gelatine. Houssay (1930) attributes to a proteolytic enzyme the local oedema, haemorrhage and necrosis as well as the general haemorrhagic lesions caused by venom.

The phosphatidases of venom, according to Houssay, are responsible not only for venom haemolysis but for action on the heart and upon striated muscle and kidney and also for the primary stimulant and later paralysant effect of application of venom to the floor of the fourth ventricle.

Snake venoms possess no diastatic action. They do not hydrolyse

starch, inulin or glycosides, nor can they invert cane sugar. The attribution of the various activities of snake venom, which we have discussed, to specific ferment actions must remain uncertain until these complex mixtures can be fractionated and the various components isolated.

THE FRACTIONATION OF SNAKE VENOMS

The conditions under which fractionation is carried out should be such as to render it unlikely that any active fractions obtained have been split off chemically from a large complex molecule or that these active fractions have themselves been altered chemically in the course of fractionation.

Destruction of active constituents by heat or other agents or apparent removal by adsorption (unless active fractions are recoverable by elution) cannot be accepted as evidence of the presence of separate active constituents in venom. Such changes in behaviour might be due to chemical alterations in active groupings of a single complex.

So far as the Australian venoms are concerned not very much has been accomplished, though a good deal of effort has been directed to this difficult problem. The use of heat, though it causes preferential destruction of some venom constituents, for example, thrombins and kinases, also causes loss of activity of other constituents. Dialysis through proxylin membranes does not give quantitative separation, since with membranes sufficiently permeable to permit the passage of proteoses, some protein coagulable by heat also passes through. Precipitation by dialysed ion or by salts of heavy metals does not yield satisfactory results, since proteose is adsorbed to the precipitates and cannot be removed by washing.

Martin and McGarvie Smith (1892) removed the coagulant-activity from black-snake venom by precipitating the coagulable protein by heating the venom to 90°C. or by denaturing the dry venom by prolonged contact with a large volume of absolute alcohol. Later, Martin (1896) separated the coagulable proteins by ultra-filtration at high pressure through filters impregnated with gelatine. The toxic filtrate so obtained had no coagulant activity and had lost the haemorrhagic and haemotoxic properties of the venom.

By extraction of the dry venom of the death adder with 45 per cent

alcohol at low temperatures it was possible to separate it into alcohol-soluble and alcohol-insoluble fractions without denaturation of the coagulable protein and without any loss of toxicity (Kellaway, Freeman and Williams, 1929). Though the separation of the heat coagulable proteins from the proteoses was not complete, it was sharp enough to allow of deductions concerning the distribution of the toxic constituents of the venom.

Death-adder venom has powerful curari-like and cytolytic actions. It is feebly haemolytic, weakly anti-coagulant *in vivo* and *in vitro*, but in high concentrations *in vitro* a feeble coagulant action can be demonstrated. It causes an immediate but transitory fall of blood pressure, when injected intravenously, and has a stimulant action upon isolated plain muscle.

The alcohol-soluble fraction, approximately four-fifths of the weight of the venom, contained less than 7 per cent of protein coagulable by heat. It possessed almost all the curari-like and anti-coagulant properties of the venom; it also caused the typical fall of blood pressure produced by the whole venom when injected intravenously.

The alcohol-insoluble fraction had no curari-like or anti-coagulant action; it possessed the feeble coagulant action of the whole venom which can only be shown *in vitro*.

The haemorrhagic and haemolytic actions of the venom and its stimulant effect on plain muscle were present in both fractions.

The application of this method to coagulant venoms effected very incomplete fractionation. Holden (1933) tested quantitatively the high pressure filtration method of Martin but found that it was not suitable for the preparation of venom freed from coagulant activity, because, when the percentage of this active agent was reduced in the filtrate to 1 per cent of that in the whole venom, the proportion of other toxic constituents was reduced to about half.

Holden then tried various adsorbing agents. Of these the most efficient appeared to be barium carbonate and he was able to prepare tiger-snake venom containing only 0.05 to 0.06 per cent of the coagulant activity of the whole venom without appreciable loss of other toxic constituents in the venom. The active coagulant could not be recovered from the adsorbent and it is probable that it was destroyed either at the surface or by the passage of carbon dioxide (Macfarlane

and Barnett, 1934) through the solution to bring mixture of venom and adsorbent to the optimal pH.

In recent years the adsorption methods developed by Willstaetter and by Waldschmidt-Leitz have been applied to the separation of the ferments of snake venoms.

Hansen (1931), for example, has concentrated the proteolytic enzyme of *Agkistrodon piscivorus* four times and those of *Crotalus adamanteus* and *Crotalus horridus* five times by adsorption with aluminium phosphate and subsequent elution.

Dunn (1934) working with the venom of *Crotalus adamanteus* has separated an active "cephalinase," with strong haemolytic but no proteolytic activity, by precipitation with 95 per cent alcohol of the filtrate obtained after removing the heat coagulable protein. In respect of its specific ferment action this fraction had five times the potency of the original venom. The haemorrhagic properties of the venom did not reside in this fraction.

The shock-producing factor was present in the filtrate after precipitation of coagulable protein, but was soluble in alcohol.

Dunn also found that it was possible selectively to adsorb cephalinase with aluminium hydroxide C (Willstaetter and Kraut, 1923) which had been aged 8 months. It is not clear from Dunn's experiments whether the proteolytic enzyme so obtained is identical with haemorrhagin.

The venom has still another activity which can be removed by adsorption, though it has not been recovered by elution, namely, the power of converting haemoglobin into methaemoglobin.

SNAKE VENOMS IN THERAPY

It might have been anticipated that substances with such manifold toxic effects would find a place in the treatment of a variety of maladies. Together with a host of valueless and a few useful remedies, they are to be found in oriental pharmacopoeias. For many years they have occupied a distinguished position in the homoeopathic system, being recommended for the treatment of a host of diseases. In allopathic medicine they have enjoyed, and still enjoy, a not inconsiderable vogue.

In 1931 Peck and Sabotka found that injection of the venom of the

moccasin (*Agkistrodon piscivorus*) made rabbits refractory to Swartzman's phenomenon—an acute focal purpura produced by a toxic body common to various bacterial groups. The venom of the North American copperhead (*Agkistrodon mokasen*) also induced this refractory state, but venoms of the genera *Crotalus* and *Bothrops* failed to do so.

Different samples of moccasin venom had variable potency in this respect and the factor responsible was independent of the haemorrhagic and curarizing constituents of the venom.

This action of moccasin venom has been applied by Peck and coworkers (1933–1935), Dack (1935) and others to the treatment of haemorrhagic diseases. In a concentration of 1:3000 the venom was given in an initial dose of 0.2 cc., increasing to 0.4 cc. twice weekly for prolonged periods. Patients who became sensitive were desensitised by a series of minute doses and the treatment was continued. According to these authors it has been efficacious in functional uterine bleeding, in epistaxis and haematuria in the Henoch-Schönlein syndrome, in thrombocytopenic purpura, in Osler's disease (multiple hereditary telangiectasis), and in haemoptysis from bronchiectatic cavities.

Another still more recent application is the use of coagulant venoms as local haemostatics in intractable bleeding. This is due, in the first place, to Macfarlane and Barnett (1934), who at Hartridge's suggestion applied it in haemophilia. Haemophilic blood which normally clotted in from 20 to 45 minutes could be clotted firmly in 17 seconds by a 1:10,000 dilution of the venom of the Daboia, *Vipera russellii*. In this strength the venom was used successfully in the treatment of haemorrhage in haemophilia following dental extraction and tonsillectomy, in epistaxis and in oozing from abdominal wounds. Rosenfeld and Lenke (1935) have used for this purpose the venom of the Australian tiger snake and in a careful study have shown its efficiency as a local haemostatic in a variety of haemorrhagic conditions, after trial and failure of other methods of haemostasis.

As regards the other therapeutic applications of snake venoms, we stand upon less certain ground. Monaelesser and Taguet (1933), and Laignel-Lavastine and Koressios (1935), have explored the use of cobra venom both for the destruction of neoplastic growths and as an analgesic for the intractable pain of cancer.

These studies suggested that in a proportion of patients the venom had a retarding influence upon the development of neoplasms and had a definite value in combating pain which otherwise needed for its relief the exhibition of morphin.

Calmette, Saenz and Costil (1933) and several other workers have tested the influence of this venom upon experimental and spontaneous neoplasms in animals. Some inhibition of growth and even regression has been observed, but on the whole the evidence for the value of cobra venom as a specific inhibitory and retarding agent for neoplastic growths is not impressive. Even its value as an analgesic has been called in question. Lavedan (1935), for example, who treated a series of 51 cases of cancer, found that it was without effect upon the evolution of the disease and that its action in relieving pain was inconstant.

There is, however, some evidence for the value of cobra venom as an analgesic and, discounting the psychological effect of a new remedy, its paralysing effect upon sensory nerve endings, which will be discussed in the succeeding lecture, affords reasonable ground for a belief in its efficacy.

Finally, the use of viperine venoms has been advocated for the treatment of epilepsy. Sufferers from epileptiform fits have been bitten by poisonous snakes and have subsequently remained free from seizures for long periods. Possibly some of these persons were examples of hysteria rather than of epilepsy. Close investigation is necessary before they can be accepted as genuine cases. Though the bite of a viper with severe consequent symptoms might well result in the cure of an hysterical patient, this accidental non-specific therapy might be equally efficacious in genuine epilepsy of allergic origin.

Spangler (1927) has utilised *Crotalus* venoms for this purpose and also for the treatment of asthma, controlling the dosage by the resulting eosinophilia.

A commercial preparation has been put on the market by a layman as a much vaunted remedy for epilepsy, chorea and for some functional nervous conditions. It is extremely difficult to assess the value of much of the evidence which has been brought forward in support of these claims; and there is no published record of a fully controlled test of its value in well authenticated cases of epilepsy.

Finally, it should be borne in mind that snake venoms are not harm-

less remedies and that our knowledge of their constitution is insufficient to justify the use of such complex mixtures without good evidence of their therapeutic value.

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SNAKE VENOMS

II. Their Peripheral Action[1]

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I. CURARI-LIKE ACTION AND OTHER RELATED PERIPHERAL EFFECTS

A common cause of death in mammals poisoned by the venoms of the *Colubridae* is asphyxia resulting from failure of respiratory movements. Is this due, as was thought by many of the early workers on snake venom, to direct action on the central nervous system or does it result from a curari-like paralysis of the muscles of respiration?

Many snake venoms have long been known to possess curari-like properties, but Ragotzi (1890) was the first to recognise the importance of this peripheral action of cobra venom and denied that there was any evidence of its central action. He observed respiratory movements of the *alae nasi* in animals under artificial respiration after the diaphragm and costal muscles had been paralysed by cobra venom, and put this forward as evidence that the central respiratory mechanism was still active, though the muscles of respiration were paralysed.

Arthus and his pupils (1910–12) showed that several Indian and Australian colubrid venoms exhibited this activity and that some of them could facilitate the action of curari, when this was administered in dosage insufficient by itself to cause curarization.

Cushny and Yagi (1918) supported Ragotzi's view regarding the peripheral action of cobra venom. They noted reflex movements of the diaphragm in animals under artificial respiration after poisoning with cobra venom and regarded these Hering-Breuer reflexes as indicating the continued activity of the respiratory centre.

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These observations suggested that the action of colubrid venoms, and of cobra venom in particular, in paralysing respiratory movement is peripheral and not central, but recently more decisive proof has been offered that many of the venoms of the *Colubridae* can kill by their curari-like action without serious impairment of the central respiratory mechanism.

Miss Williams, Cherry and I (1932) have shown that almost all the Australian snake venoms and the most deadly of the Indian colubrid venoms, those of the dreaded sea snake *Enhydrina schistosa*, the cobra (*Naia naia*), the hamadryad (*Naia hannah*) and the common krait *Bungarus coeruleus* can cause death by peripheral action. Animals were anaesthetised with sodium amytal or dial, the trachea was cannulised and the fourth root of the phrenic nerve in the neck was placed upon electrodes connected with an amplifier, the output from which was fed to a loud speaker. In some experiments, instead of using the fourth root of the phrenic in the neck, the electrodes connected with the amplifier were placed, at a later stage of the experiment, on the phrenic nerve in the thorax. In this way we were able to listen in to the amplified descending motor action currents in the phrenic nerve. Venoms without coagulant action were injected intravenously in single or divided doses in amounts sufficient to cause failure of respiratory movements. When this occurred, the action currents became asphyxial in type; artificial ventilation was now applied and if this were continued, strong descending action currents in the phrenic nerve were audible for from $1\frac{1}{2}$ to 6 hours, though no sign of respiratory movement could be observed when artificial respiration was temporarily interrupted.

Immediately after the cessation of natural breathing the thorax was opened and the phrenic nerve of one side was tested by faradic stimulation. The diaphragm was not always completely curarized, but some impairment of the response to weak indirect faradic stimulation was noted, and in these animals, at a later stage, curarization of the diaphragm became complete.

In other experiments venom was given intravenously or, if it possessed coagulant properties, subcutaneously to unanaesthetised animals. When natural respiration ceased, the animals were kept alive by artificial ventilation under an anaesthetic and the continued activ-

ity of their central respiratory mechanism, as indicated by changes in the descending action currents in the phrenic nerve, was demonstrated during several hours. Excess of ventilation abolished the descending action currents and insufficient ventilation increased the intensity of the discharge.

In these experiments the bulbar nuclei controlling respiration either were not damaged at all or, at least, were not damaged sufficiently by colubrid venoms in the doses used to account for death by central action. These results do not exclude minor central effects of venom nor the possibility that, when the bulbar nuclei are poisoned by the prolonged asphyxia induced by the inefficient action of the wholly or partially curarized muscles of respiration, the presence of venom in the circulation may sometimes be a determining factor in causing central respiratory failure, from which recovery takes place when, by artificial ventilation, the centres are again supplied with oxygenated blood.

Experiments upon amphibians have shown that nearly all snake venoms possess, to some extent at least, this curari-like action, though colubrid venoms are much more potent than viperine venoms in this respect. In frogs, death does not usually result from curarization, partly because they can still breathe through their skins when their respiratory muscles are paralysed, and partly because some species are more sensitive to other actions of snake venoms.

For these reasons Houssay, Negrete and Mazzocco (1922) and Holden and I (1932) have used isolated nerve muscle preparations set up according to the *in vitro* method of Claude Bernard for the study of the curari-like property of snake venoms. This method has the additional advantage that the observations can be made quantitative. In our experiments the venom of the Indian cobra proved to be by far the most potent of all the venoms investigated, being active in a concentration of 1:200,000. Other Indian and Australian colubrid venoms caused curarization in concentrations of 1:10,000 to 1:4000, but the two viperine venoms we tested, those of *Echis carinata* and *Crotalus adamanteus*, required a concentration of 1:2000 to produce complete curarization within 5 hours. The observations of Houssay and his colleagues placed some of the South American viperine venoms, those of *Crotalus terrificus* and some members of the genus *Bothrops*, in the more active group.

This peripheral action of snake venoms, though it has a general resemblance to that of curari, presents certain important differences. One of these is its irreversibility.

Arthus (1910) showed that curarization by snake venoms was irreversible, except by the aid of antivenene. In rabbits curarized with cobra venom he observed the return of natural respiratory movements, sufficient to maintain life, within $2\frac{1}{2}$ to 6 hours after the administration of antivenene.

In curarization by the venoms of the Australian tiger snake and copperhead reversal by antivenene is much more difficult to achieve and, even when massive doses of monovalent antivenenes are administered, the animals have to be kept alive under artificial ventilation for from 20 to 29 hours before adequate natural breathing is re-established. This is partly due to the longer period occupied in the development of curarization, which allows the venom to become so fixed in the tissues that neutralization by antivenene is difficult, and partly to another peripheral action of the venom presently to be described which is irreversible by antivenene.

Another important difference between this peripheral action of snake venoms and that of curari is the failure of eserine to antagonise curarization by venoms (Cushny and Yagi (1918)).

The exact nature of the curari-like action of venoms still remains to be investigated. Dale, Feldberg and Vogt (1936) have shown that the motor impulse is transmitted to skeletal muscle by the liberation of acetylcholine and that after curari, though acetylcholine is still liberated, the muscle no longer responds to it. In the light of these experiments the question arises whether the snake venoms act in the same way as curari, or whether they inhibit the liberation of acetylcholine.

Apart altogether from their action on the transmission of nerve impulses to skeletal muscle I have been able to demonstrate still another peripheral action of snake venoms (1934)—that upon the transmission of sensory nerve impulses from tactile and proprioceptive endings. By amplification of the action currents from the tactile endings in the skin of the frog and in the peroneal nerve from the toe-muscle preparation of Matthews (1931), it was shown that venoms in concentrations of 1:10,000 to 1:1000, though they were without effect upon the nerves themselves, cause paralysis of these endings within 2 or 3 hours.

so that action currents are no longer set up in the nerves by appropriate stimulation of the end organs. Of the venoms studied, that of the cobra was easily the most active and was effective upon the tactile skin endings in a concentration of 1:100,000. Curari is much less active in this respect. It has but little effect upon tactile skin endings and an active sample, which paralysed the transmission of motor impulses in a concentration of 1:100,000 in between 2 and 4 hours, required about the same time in a concentration of 1:1000 to abolish the action currents from muscle spindles.

The action of venoms on the transmission of sensory impulses is trivial compared with that of a good local anaesthetic, percain for example, which within 12 minutes causes complete paralysis of the sensory endings of the skin in a concentration of 1:100,000.

It is of some interest that "mussel poison," which during the summer months is irregularly present in mussels on the Pacific coast of this continent, has an extremely powerful action upon the transmission of sensory nerve impulses, being effective in the abolition of action currents from tactile endings in a concentration of one in 2 millions within 60 minutes, and in one in 1 million within 12 minutes (Kellaway, 1935).

In addition to these actions upon motor and sensory endings, snake venoms have still another peripheral action. They directly paralyse the muscle itself.

The recognition of snake venoms as muscular poisons is largely due to the work of Houssay, Negrete and Mazzocco (1922), who in experiments with amphibian nerve muscle preparations found, that with some venoms, before curarization became complete, the irritability of the muscle to direct stimulation fell off greatly, compared with that of control muscle in saline. With much higher concentrations of venom, fibrillary contractions and contracture were produced in isolated sartorius preparations. They related these direct effects upon muscle to the haemolytic activity of the venoms as determined by haemolysis of canine red corpuscles in the presence of homologous serum, and showed that those venoms which were most active in these respects caused also the greatest imbibition of water by frog skeletal muscle *in vitro*.

Houssay has suggested that this direct action of venom upon skeletal

muscle is due to the phosphatidase, which causes haemolysis and which, acting on the lipoid constituents of muscle cells, induces changes in permeability which lead to swelling and ultimately to loss of irritability. In this connection it is of interest to recall that snake venom haemolysis is preceded by swelling of the erythrocytes (Mitchell and Reichert (1886), Essex and Markowitz (1930), Kellaway and Williams (1932)).

Holden and I (1932) have observed this loss of irritability to direct stimulation with a wide range of Indian and Australian colubrid venoms. In general, those which were most powerfully haemolytic and which caused the greatest amounts of imbibition in isolated frog muscle were also most potent in abolishing the irritability of frog muscle to direct stimulation. Nevertheless, some venoms, which have a strong direct action upon the irritability of muscle, are only feebly haemolytic and do not cause much swelling of isolated skeletal muscle *in vitro*. Tiger-snake venom, for example, in extremely minute concentrations acting for a long time, causes pronounced loss of irritability of mammalian muscle *in vivo*, which, once established, cannot be reversed by antivenene. The venom is only feebly haemolytic and causes very slight imbibition of water by isolated amphibian skeletal muscle.

These apparent exceptions do not necessarily destroy the validity of Houssay's theory, since the venoms in question do possess some haemolytic powers and also cause slight imbibition of water in isolated frog muscle. On the other hand, it is possible that we are here concerned with an effect of a different nature.

II. CENTRAL ACTIONS OF SNAKE VENOM

The chief evidence relied upon by those who maintain that the curari-like action of colubrid venoms is unimportant, and that the venoms have a primary action on the central nervous system and particularly upon the medullary nuclei, is that in envenomed animals, when respiratory movements have ceased, curarization of the diaphragm is often incomplete, that in the early stage of poisoning the rate and extent of respiration are augmented, and that, as Elliot (1905) showed, dry venom applied to the floor of the fourth ventricle

of the anaesthetised animal caused death by rapid failure of respiration without any curarization of the diaphragm.

The theory of a central action has also been applied to explain other effects of snake poisoning. For instance, Chopra and Iswariah (1931) have shown that the intravenous injection of small doses of cobra venom sometimes causes a rise of blood pressure accompanied by peripheral vasoconstriction and that these phenomena do not occur in spinal preparations in which the brain has been destroyed.

Their evidence concerning the central action of cobra venom upon respiration is less convincing. In artificially ventilated animals they studied the effects of injection of venom by recording the movements of the costal wall and of a strip of diaphragm containing the endings of the left phrenic nerve. Small doses of venom caused acceleration of diaphragmatic movements and increase in tone of the muscle, while larger amounts produced cessation of respiration with spasmodic contraction of the diaphragm. That these increased diaphragmatic movements were not due to direct peripheral action on the muscle was shown by freezing or cutting the phrenic nerve.

Cherry, Miss Williams and I have also sought evidence of the central action of colubrid venoms. In semi-isolated head preparations in cats we observed the effects upon the femoral blood pressure and on the respiratory movements. The head was supplied, by a Dale-Schuster pump, with defibrinated and hirudinised blood oxygenated by an artificial lung. Injection of death-adder venom into the head circulation in a concentration of 0.1 mg. per cubic centimeter caused loss of corneal reflex and cessation of diaphragmatic movements within a minute. There was an immediate rise of pressure in the head circulation and a simultaneous dramatic fall in the circulation in the body. These effects may have been due to vasoconstriction in the head circulation attended by a carotid sinus reflex, causing cessation of respiration and fall of blood pressure in the body. We attempted to cause central failure by the application of Australian venoms in moderate concentrations to the floor of the fourth ventricle. This did not occur, but we observed some central action of an opposite kind. Invariably the application of venom was initially attended by a gradual acceleration and deepening of respiration but with very little effect on the blood pressure. For one venom at least, that of *Crotalus*

terrificus, there is evidence of strong central action. Houssay and Hug (1928) have shown this in the isolated head preparation supplied with blood from a second animal and connected with its own body only by the vagus nerves. Strong respiratory effects were observed in the isolated head and vagal actions in the body following the administration of venom to the donor. These effects occurred whether the pressure in the donor dog rose or fell and were due to the direct action of this venom on the vagal and respiratory nuclei in the bulb.

So far as the venoms of the *Colubridae* are concerned, apart from early stimulation of respiration and the rise of blood pressure in the case of cobra venom, which may probably be attributed to central action, we may conclude that these venoms do not cause central respiratory failure by direct paralysant action. It is still possible that they may sometimes exert an effect upon centres inadequately supplied with oxygen sufficiently damaging to cause failure of respiration before the peripheral curarization which is the primary cause of asphyxia has fully developed.

III. CIRCULATORY FAILURE IN SNAKE-VENOM POISONING

The most frequent cause of death after bites by viperine snakes is not curari-like paralysis, but profound circulatory failure. In the late stages of poisoning by the venoms of Australian snakes this may also be a dominant feature and with other colubrid venoms circulatory effects may also play a part in causing a fatal issue.

Circulatory failure may be due to failure of the heart, to peripheral vasodilation, to obstruction in the pulmonary circulation or even to constriction of the hepatic veins. These effects may be aggravated by increased permeability of the vessels, causing loss of fluid from the circulation either more generally at the periphery, or into special organs like the lung or liver.

In poisoning by different snake venoms the symptomatology varies greatly, and unfortunately our knowledge of the circulatory changes which occur, both with different venoms and with individual venoms in different species of experimental animals and in man, is still very incomplete.

An instance of circulatory failure in which obstruction in the pulmonary circulation plays the leading rôle is afforded by the action of

cobra venom injected in large doses intravenously (Feldberg and Kellaway[2]). Such an injection causes an almost immediate fall of the systolic blood pressure, the pulsatory oscillation of the mercury manometer dwindles to nothing and, if the thorax is opened, the right heart is found to be tensely distended with blood, while the left heart is empty. That this is due to pulmonary constriction is shown by a rise of pressure in the pulmonary artery which precedes the fall of systemic pressure (fig. 1). The increased pulse oscillations in the

FIG. 1. EFFECT OF INTRAVENOUS INJECTION OF 8 MG. COBRA VENOM UPON ARTERIAL BLOOD PRESSURE FROM CAROTID (A.P.) AND PULMONARY ARTERY (P.P.)
Time in ½ minutes

pulmonary artery indicate the strong effort of the overfilled right heart to overcome the obstruction. The pulmonary pressure actually becomes higher than the pressure in the carotid. In animals in which the obstruction is overcome and the fatal issue delayed, the lungs show extensive haemorrhages and haemorrhagic oedema. By drainage of a lung in this condition after amputation at the hilus we have collected as much as 30 cc. of fluid in the course of 40 minutes. Even

[2] Unpublished studies.

after this loss of fluid the lung was still twice as heavy as that of the other side which had been tied off before the injection of venom.

With other venoms peripheral dilatation plays a more important part. Essex and Markowitz (1930) have studied the action of the venoms of *Crotalus atrox* and *Crotalus horridus* and have shown that the profound fall of blood pressure almost immediately following the intravenous injection of these venoms must be attributed mainly to vasodilation in the body musculature. They excluded central action by experiments upon the decapitate preparation and showed that obstruction in the pulmonary circulation was trivial and in the hepatic circulation absent, since the pulmonary blood pressure rose only slightly during the fall of general blood pressure and the effect was not altered in animals from which the liver had been removed. The fall of blood pressure was not due to any direct action of the venom on the heart, because there was never any immediate diminution in the output of the isolated heart-lung preparation, when the venom was administered in concentration equivalent to that necessary to cause a fall of blood pressure in the intact animal.

Plethysmographic records showed pronounced vasodilation in the limbs. Essex and Markowitz were able to show that the initial precipitous fall of blood pressure was not accompanied by vasodilation in the abdominal viscera, though this occurred after some minutes with an irrecoverable increase in the volume of these organs.

Though the initial fall of blood pressure seems therefore to be due mainly to peripheral vasodilation, lung oedema and weakening of the heart's action evidently play a part in the later stages, for in the isolated heart-lung preparation these effects were regularly observed.

LeMessurier and I (1936) have studied the initial fall of blood pressure which occurs following the intravenous injection of small doses of the venom of the Australian copperhead. This also is chiefly due to peripheral vasodilation. It is not directly central nor mediated by carotid sinus reflexes, for it occurs in the decapitate preparation, and denervation of the carotid sinuses and section of the vagi do not impair the response. When small doses of venom were injected, simultaneous records of the pulmonary and systemic blood pressures showed no rise in the former accompanying or preceding the fall in the latter. Experiments upon isolated heart-lung preparations excluded direct

action upon the heart but within about 15 minutes the lungs became oedematous. The fall of blood pressure also occurred in eviscerate preparations with the liver excluded from circulation. In plethysmograph experiments it was attended by vasodilation of the limb and bowel, but by a very large fall in the volume of the spleen.

IV. THE LIBERATION OF HISTAMINE BY SNAKE VENOMS

Our main interest in the analysis of the fall of blood pressure due to the intravenous injection of copperhead venom was that this venom causes a fall of blood pressure from which the animal recovers and is desensitised to later injections of venom. We were struck by the similarity which this phenomenon presents to desensitisation in anaphylaxis, a similarity which is even more striking if other effects of this venom are taken into account.

Some years earlier (1929) I had studied the action of Australian venoms upon the isolated uterus of the virgin guinea-pig and had drawn attention to the resemblance of the contraction so obtained to that of sensitive plain muscle to its anaphylactic antigen. The latent interval observed following the addition of venom to the bath was of the same order as that in the anaphylactic response; a second dose was without effect and by the use of a number of small doses of venom it was possible to desensitise the plain muscle without reaction. I suggested that the action of snake venom on the cells might not be direct but indirect by the liberation of a stimulant substance like histamine.

Essex and Markowitz (1930) were also impressed by the close similarity of the circulatory effects of crotaline venoms to those caused by histamine and in acute anaphylactic shock. They actually took the precaution of showing by prolonged extraction with alcohol and biological test of the evaporated extract that histamine was not present in the venoms. They showed that crotaline venoms have other characteristic actions which resemble those of histamine and of anaphylaxis. Injected into the etherised dog they cause, after a short latent interval, a rise in the intravesical pressure. In the guinea-pig, intravenous injection results in bronchospasm not quite so regular nor so complete as is manifested in acute anaphylaxis or following the injection of histamine.

The venoms also cause contraction, after a latent interval of 30 seconds, of the isolated uterus of the virgin guinea-pig. A second dose after recovery from the first is without effect, but the muscle is still sensitive to histamine.

Finally, when pricked into the human skin in a concentration of 1:500 it causes a triple response like that caused by 1:10,000 histamine.

LeMessurier and I (1936) have drawn attention to further points of resemblance between the action of the Australian snake venoms and histamine. The vessels of the isolated ear of the rabbit respond by constriction both to histamine and to snake venoms, but in the latter case the response occurs after a long latent interval and the vessels are desensitised to further doses of snake venom, the response to histamine remaining unimpaired.

Bronchial constriction was also observed in the pithed guinea-pig following the injection of copperhead venom. This could be obtained regularly only in animals of small size and was most evident in such animals as were most sensitive to histamine. With venom there was a latent interval of nearly a minute before the full effect was observed.

It has been demonstrated that histamine is liberated in anaphylactic shock. Manwaring and his coworkers (1925) had already shown that a stimulant substance is liberated from the dog's liver into the hepatic blood in anaphylactic shock. These observations were reinforced by the experiments of Simonds and Brandes (1927) and more recently by those of Dragstedt and Gebauer-Fuelnegg (1932), who showed that the lymph from the thoracic duct of dogs in acute anaphylactic shock contained a histamine-like substance. Bartosch, Feldberg and Nagel (1932) made a more complete analysis of the effect in experiments on the perfused guinea-pig lung.

The close similarity of the reactions of venom to those of acute anaphylaxis led us to examine the possibility that this similarity might be due to the liberation of histamine by the cytolytic action of the venom.

We tested the perfusate from the isolated lungs of cats, before and immediately after perfusion with venom, upon the isolated uterus of virgin guinea-pigs which were first desensitised with snake venom. With such preparations which were capable of detecting, under the conditions which we used, amounts of the order of 0.3 γ of histamine we failed to detect histamine in the perfusate.

We also tested in the same way the lymph from the thoracic duct of dogs before and after the intravenous injection of copperhead venom and found that the lymph, after the injection, invariably exerted a stimulant action on the isolated uterus. Unfortunately, these last apparently positive results were not decisive because, in the presence of lymph, the guinea-pig uterus becomes extremely sensitive to small traces of a stimulant substance in copperhead venom against which we were unable to desensitise the plain muscle.

Feldberg and I have pursued this line of enquiry, using the methods Feldberg had already successfully applied with Bartosch and Nagel, in the demonstration of the liberation of histamine in acute anaphylactic shock in the guinea-pig.

The isolated lungs of normal guinea-pigs, artificially ventilated at 9–14 per minute, were perfused through the pulmonary artery with Tyrode solution—the outflow being collected by means of a cannula introduced into the left auricle. Fluid leaking from the outer surface of the lungs was collected by a suitably shaped sheet of celluloid placed under the lungs. The outflow fluid was collected in separate samples during the course of some hours after the injection of venom. The samples both before and after the injection were tested on the isolated small intestine of the guinea-pig which was first desensitised with snake venom. Such preparations in a 3.0 cc. bath were sensitive to 0.01 γ of histamine.

The venom when injected into the lung circulation produced immobilisation due to bronchial constriction usually within half a minute to a minute and a half. Later the lung became tense and swollen, showed patches of glassy appearance, and fluid exuded from its external surface.

Up to the present three venoms have been studied, those of the Australian copperhead (*Denisonia superba*), of a North American rattle snake (*Crotalus atrox*) and of the Indian Cobra (*Naia naia*). All these have been shown to liberate an active stimulant substance from the lung. This substance has been identified pharmacologically with histamine by its effects on the guinea-pig intestine and on the blood pressure and suprarenals of the cat. It caused contraction of the isolated guinea-pig intestine (Fig. 2), and in the cat a fall of blood pressure which was not abolished by atropine (Fig. 3), and an output

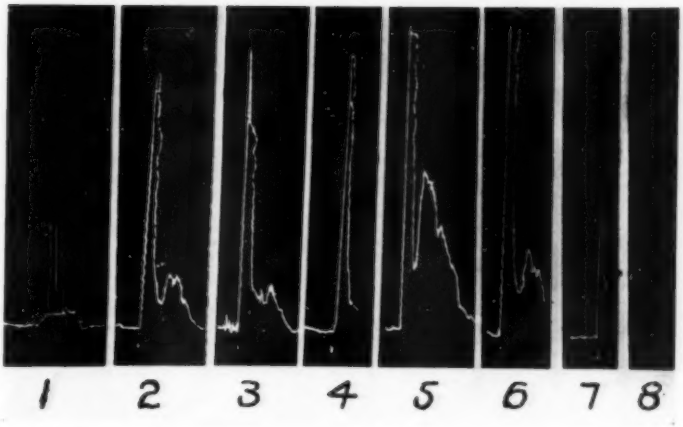

FIG. 2. EFFECT OF LUNG PERFUSATE ON ISOLATED GUINEA-PIG'S SMALL INTESTINE

(*1*) 0.5 cc. perfusate before venom. (*2*), (*3*), (*5*) and (*7*) 0.2 cc. perfusate from succeeding ½ hour samples after injection into pulmonary artery of 9 mg. cobra venom. (*4*), (*6*) and (*8*) 0.2 cc., 1:3.3 millions, 1:2.5 millions and 1:10 millions histamine, respectively.

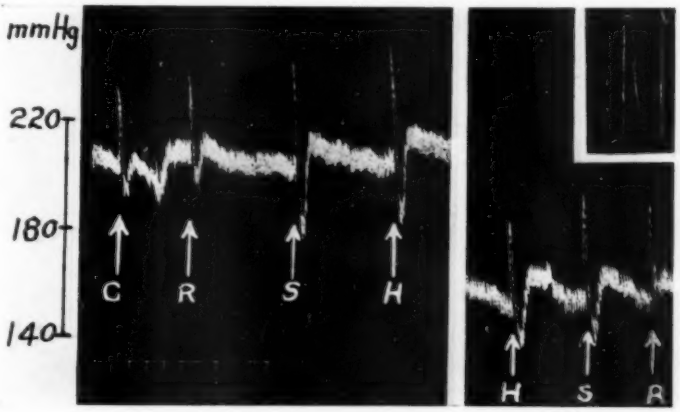

FIG. 3. TITRATION OF LUNG PERFUSATE UPON ARTERIAL BLOOD PRESSURE OF EVISCERATED CAT AND GUINEA-PIG INTESTINE

Time in ½ minutes. Amounts of 1.0 cc. injected; at *C*, perfusate before venom; at *R*, Ringer's solution, at *S*, sample collected during the second hour after 1.5 mg. copperhead venom injected into the pulmonary artery. At *H*, histamine 1:2 millions. In the right hand panel the titration is repeated after 2 mg. atropine. Top right hand corner, effect of 0.2 cc. S., and 0.2 cc. histamine 1:2 millions.

of adrenaline from the suprarenals. These are characteristic reactions of histamine; but even more convincing evidence of identity is afforded by the fact that the reactions in all three tests of any given sample corresponded quantitatvely with those produced by one and the same dose of histamine. Still further evidence of the identity of this active substance with histamine is provided by the quantitative estimations, presently to be described, which can only be interpreted on the assumption that the substance found in the outflow fluid is part of the histamine which is normally present in the lung.

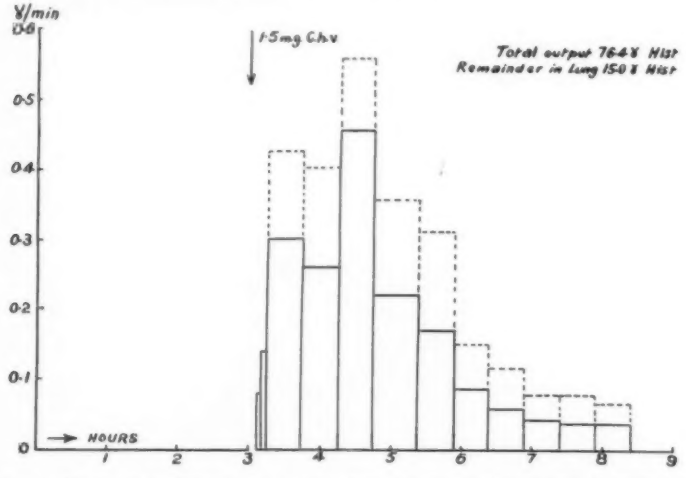

FIG. 4. HISTAMINE OUTPUT IN γ PER MINUTE FROM PERFUSED GUINEA-PIG'S LUNG AFTER 1.5 MG., COPPERHEAD VENOM

The areas enclosed by dotted lines represent histamine in the "outside" fluid

The liberation of histamine has been studied in detail in experiments with the venom of the Australian copperhead. The output lasts throughout a long period and reaches a maximum after half an hour, one, two or three hours, according to the dose injected, and then gradually falls off. The results of one experiment are illustrated in Figure 4, which shows the output of histamine following the injection of 1.5 mg. of copperhead venom, the ordinates being the amounts in γ liberated per minute, and the abscissae, the time in hours.

In this experiment one objection which might be raised against these

long continued lung perfusion experiments is met, namely, that histamine might appear in the venous outflow without the injection of venom. The lung was perfused for three hours before the venom was injected and the samples collected during that time contained no detectable histamine.

These snake venoms can almost completely empty the store of histamine in the lung. In this experiment the total output was 76.4 γ

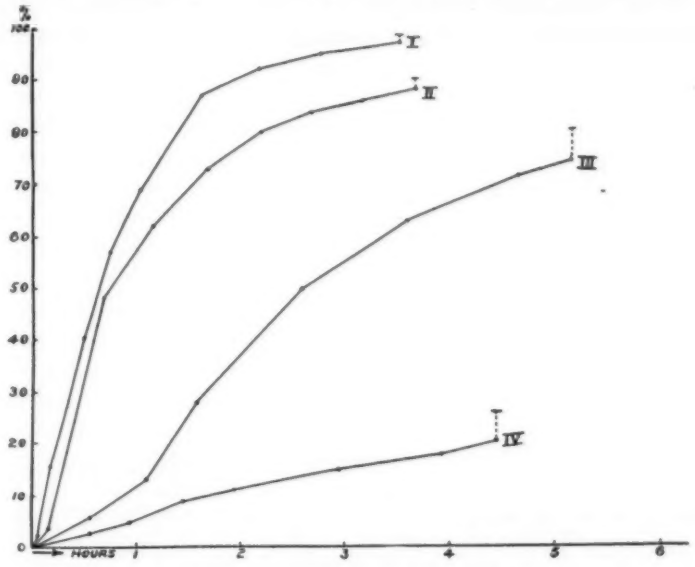

FIG. 5. HISTAMINE OUTPUT EXPRESSED AS PERCENTAGE OF TOTAL LUNG HISTAMINE FROM SINGLE LUNG

I, after 10 mg.; *II*, after 5 mg.; *III*, after 1.5 mg.; *IV*, after 0.3 mg. copperhead venom.

and an extract made from the lung at the end of the experiment yielded only a further 15 γ of histamine. More than 80 per cent of the histamine in the lung had been found in the perfusate. With larger doses the output was still greater.

There was some irregularity in the amounts of histamine liberated from the lung which could not be related to the size of the dose of venom. In some experiments even with larger doses smaller amounts

of histamine were liberated, 30, 20 or 15 γ. This was found to depend upon the smaller amounts of histamine available in the lungs.

It has been shown that in a guinea-pig the individual variation in the histamine content of the lungs is very great, but variation between the content of the right and the left lung is negligible. We, therefore, in further experiments perfused one lung only, using the other as a control and estimating its content of histamine.

When the amount of histamine in the lungs was taken into consideration, its liberation was found to be dependent only upon the dose of

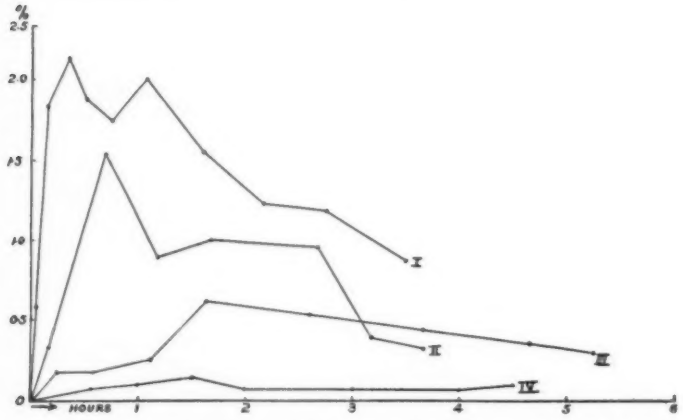

FIG. 6. OUTPUT OF HISTAMINE IN SAME EXPERIMENTS AS IN FIGURE 5 PLOTTED AS PERCENTAGE PER MINUTE OF HISTAMINE REMAINING IN THE LUNG IN SUCCESSIVE SAMPLES

venom injected. This is illustrated in Figure 5, in which the amounts liberated are plotted as percentages of the total amount available as ordinates, against the times as abscissae. With a large dose of copperhead venom (10 mg.) more than half of the available histamine was liberated in the first hour and 97 per cent within $3\frac{1}{2}$ hours. With smaller doses of copperhead venom the liberation was slower and less complete. It appears, at first sight, that the difference between small and large doses consists merely in difference in the rate of liberation, and that if the perfusion were long enough continued all the histamine would be liberated whatever the size of the dose.

This, however, is not the case. If the output per minute is plotted, not as a percentage of the total amount available but, as in Figure 6 as a percentage of the amount remaining in the lung at the time of each successive sample, it becomes apparent that, as the perfusion proceeds, the amount of histamine set free diminishes in relation to these remainders. The permeability of the tissues to histamine must therefore decrease during the course of the perfusion. With large doses in the early stages, as in this experiment, more than 2 per cent of total lung histamine may diffuse into the perfusate within one minute. After 3½ hours, less than 0.9 per cent per minute of the then remaining histamine diffused out.

Some further evidence concerning the nature of the process is afforded by the demonstration of a gradient in the concentration of histamine from the lung tissue to the outflowing fluid. If the fluid from a perfused lung, excised some hours after the injection of copperhead venom, is allowed to drip from it and the histamine content of the fluid is estimated, this will be found to be less than that in the lung itself, but greater than that in the terminal samples of perfusate. Furthermore, this drainage fluid can be collected in successive fractions which show a similar gradient. The histamine found in this drainage fluid is indicated in Figure 5 by the vertical dotted lines at the ends of the curves.

Histamine output varies with different venoms. With the same dose of cobra venom the total amount of histamine liberated is less than with the venom of the Australian copperhead. If the total output of histamine from a dose of 9 mg. of cobra venom be compared with that of 1.5 mg. of copperhead venom which yields about the same total amount of histamine, it will be seen (Fig. 7) that the output with cobra venom reaches its peak more rapidly and ceases much sooner. These differences may not be due to actual differences in the process of liberation of histamine from the cells but may depend on variations in those conditions which determine its diffusion from the tissue spaces into the perfusate.

Recently similar experiments have been performed upon the cat's lung with even more striking results.

In one experiment, for instance, the right lung of a cat weighing 2.4 kg. was perfused and 18 mg. of cobra venom were injected. The

perfusate during the ensuing 3 hours contained 215 γ of histamine; from the drainage fluid during 30 minutes another 23 γ were collected. The lung then yielded only another 30 γ by extraction. The lung of the other side weighed 7.3 gm. and yielded 243 γ of histamine by extraction.

Further experiments have shown that the injection of venom causes increased concentration of haemoglobin and therefore that, as in histamine shock, fluid passes from the blood into the tissue spaces. In experiments in cats following the injection of 2.0 mg. per kilogram

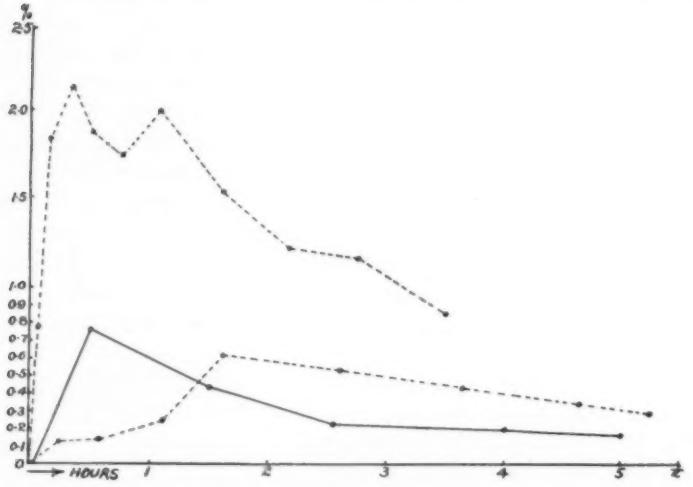

FIG. 7. OUTPUT OF HISTAMINE AFTER INJECTION OF 9.0 MG., COBRA VENOM (CONTINUOUS LINES) COMPARED WITH *I* AND *III* (DOTTED LINES) OF FIGURE 6

of copperhead venom the calculative fluid loss within 50 minutes varied from 40 to 70 cc. It remained uncertain what part of this loss might be due to oedema of the lungs, and an approximate estimate of this was obtained by comparing the weights of the right and left lungs, the left being removed before and the right after the injection of venom. With doses of copperhead venom of this order, oedema of the lungs was found, in preliminary experiments, to account for from 5 to 35 per cent of the total loss of fluid from the circulation, the remainder being presumably due to a general increased permeability of the capillaries.

In the light of these observations there can be no doubt that histamine is liberated by snake venoms, and we may be certain that it plays a part in the varied symptomatology of snake-venom poisoning, and that the contraction of the plain muscle and the initial fall of blood pressure which follows intravenous injection of venom are due to the liberation of histamine.

The liberation of histamine is, however, only one manifestation of the cytolytic activity of the venoms. The gross damage to the cellular tissues must contribute to the fatal outcome and is responsible for some of the differences observed between poisoning by histamine and poisoning by snake venoms.

Some indication of this cellular damage was given in our perfusion experiments by estimation of the approximate amount of coagulable protein in the outflowing fluid from the lung by Esbach's reagent. Generally speaking, those samples which have the highest histamine concentration show also the largest amount of coagulable protein and the concentration of proteins increases with the dose of venom.

There is one further factor which must be taken into consideration. The function of histamine is that of a local tissue hormone, and the organism is protected against its diffusion into the blood stream in effective concentrations. The experiments of Best and McHenry (1930) have demonstrated that there is an enzyme capable of destroying histamine—"Histaminase," which is present in many tissues, but *in vitro*, is rather slow in its action, and it seems likely that some additional protective mechanism prevents the easy entry into the blood stream of histamine liberated into the tissue spaces. The chief effects of histamine must therefore be produced at the site of liberation.

Differences in symptomatology in poisoning by snake venoms and by histamine are readily explained if the action of histamine at its site of liberation be taken into account.

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A PUZZLING CASE OF OBSTIPATION APPARENTLY DUE TO MESENTERIC ADENITIS

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Submitted for publication November 6, 1936

This single case is reported since it furnishes an instance of apparent success in overcoming obstipation by the operative removal of calcified lymph glands in the lower ileum and ascending colon.

CASE REPORT

M. E. H. *First Admission.* A young woman of 23 came to the Johns Hopkins Hospital on March 3, 1936, complaining of obstinate constipation associated with paroxysms of intense abdominal pain.

Family History: Her father died at 54 years of age of "cancer of the ribs." Her mother, aged 52 years, has rheumatism. One brother died of a gastric ulcer when 28 years of age. Two brothers and two sisters are living and well. There is no history of tuberculosis, diabetes, or cardiorenal disease in the family.

Past History: She has had the usual childhood diseases; her tonsils and adenoids were removed when she was 11 years of age. Menstruation has always been somewhat irregular. She is of a rather nervous disposition. For the past six years she has done clerical work, during the last two as a government clerk.

Present Illness: For the past seven years she has suffered from constipation, which became greatly aggravated after an appendectomy six years ago. She has tried almost every proprietary cathartic, sometimes taking four different kinds in one day, and as many as 14 "Alophen" tablets in one dose, without the desired result. Frequent enemas were also used. In spite of all this, seven or eight days would often elapse without a bowel moment. She tired easily, and felt "drowsy and dragged-out" every day. She suffered from a constant sensation of pressure in the abdomen, most marked on the right side, and for the past three months has had such severe abdominal pain that she would be forced to leave her work and lie down for an hour or two each day.

Physical Examination: A well nourished, well developed young woman of 23 years, in no obvious discomfort. A complete examination revealed nothing remarkable except some tenderness on deep pressure under the healed incision in the right iliac fossa.

Laboratory Findings: Urine and Blood Count normal. Blood Wassermann negative. Basal Metabolic Rate plus 4. Intradermal tuberculin reaction, posi-

tive. Gastric analysis normal. Roentgenographical studies of the entire gastrointestinal tract were reported as showing no abnormality, but three discrete

FIG. 1. An x-ray examination was made of the large bowel filled with barium. At this time a group of calcified mesenteric lymph nodes were seen to the right of the second and third lumbar vertebrae.

calcified shadows could be seen just to the right of the third and fourth lumbar vertebrae.

Treatment: The patient had been told that her symptoms were due to intra-abdominal adhesions resulting from the appendectomy, and she sought relief

through an abdominal operation to free these adhesions. Because of the paucity of positive physical and laboratory findings, an operation was thought inadvisable until medical treatment had been given a thorough trial. Consequently, after some improvement under dietary measures and massage she was sent home.

FIG. 2. This picture was taken two weeks after the operation at which the calcified glands were removed.

Second Admission: Two months later she returned with the constipation as pronounced as ever and, in addition, severe abdominal pain that would cause her to go to bed for an hour or more each afternoon. An exploratory laparotomy on June 11, 1936, showed no postoperative adhesions. The viscera were entirely

normal, but three distinct groups of calcified lymph glands lay close together in the mesentery at the ileocecal junction and along the first portion of the ascending colon. These glands did not actually touch or encroach on the bowel itself and were easily removed, the mesenteric edges being closed over with interrupted stitches. An uneventful convalescence followed and on the third postoperative day she had a spontaneous bowel movement. Since that time, 5 months ago, she has had a normal movement each morning, has been free from pain, has lost the constant "tired feeling," and has been mentally more alert.

The association of pain with tuberculous enlargement of the mesenteric and retroperitoneal lymph glands has long been recognized. The term, *Tabes Mesenterica*, according to de Sauvages' *Nosologia Methodica* (1), was first employed to describe this condition of the glands by Giorgio Baglivi (2) (1668–1707), Professor of Physick and Anatomy in Rome. De Sauvages' book has as one of the subdivisions of tabes, *Tabes Mesenterica Baglivi*, but the term itself was not found in Baglivi's *De Praxi Medica*, printed in Latin in 1700, and of which there are excellent English and German translations.

Bier (3), in 1892, reported the relief from abdominal pain after removal of some greatly enlarged caseous mesenteric and retroperitoneal lymph glands. Among others, Corner (4), Stark (5), Risley (6), Braithwaite (7), Randall (8), Golden (9), and Auchincloss (10) have written on the subject.

It seems almost certain that all caseous and calcified mesenteric and retroperitoneal glands are tuberculous in origin. However, enlarged lymph glands that show no gross or microscopic evidence of tuberculosis are commonly found, especially in young children, in many conditions for which the abdomen is opened. Very often acute appendicitis is suspected in these cases before operation. The patients recover spontaneously and do not suffer afterward from further enlargement of these glands, so that we are led to believe that mesenteric adenitis, which may or may not have a tuberculous origin, is a relatively common condition in children and young adults.

The calcified mesenteric glands and the positive tuberculin skin reaction in our patient indicate without reasonable doubt a tuberculous origin. Of primary interest here is the question whether the pressure and distension in the mesentery caused by these large calcified glands could be the active cause of her severe constipation and pain, pre-

sumably through pressure on the autonomic nerves leading to the lower ileum, cecum and ascending colon.

Any traction on the mesentery gives exquisite pain, as can readily be proved when a patient is undergoing an abdominal operation under a local anesthetic, and there are numerous references in the literature to abdominal pain caused by tuberculous mesenteric glands. No reference, however, has been found to enlarged mesenteric glands as a cause of constipation. Golden (9) mentions delay in the passage of barium through the lower ileum in the presence of calcified mesenteric lymph nodes, a finding that would fit well into the hypothesis that the constipation in this patient was caused by such glands.

This case offers no definite proof that her obstipation was attributable to the group of calcified mesenteric glands. Nevertheless, the relief of the patient from this symptom has been complete since operation, and it is felt that so striking a result justifies publication.

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EXPERIMENTAL STUDY OF CONGENITAL SYPHILIS, INCLUDING A STUDY OF THE INFECTIOUSNESS OF BLOOD, UTERUS AND PLACENTA OF PREGNANT RABBITS WITH EARLY SYPHILIS

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The first experimental study of the transmission of syphilis from an infected female rabbit to her offspring was made by Uhlenhuth and Mulzer (1) in 1913. They injected a pregnant doe intravenously with 10 cc. of an emulsion of an acute testicular syphiloma. The animal succumbed immediately and normal adult rabbits were successfully inoculated both with the placentae and with the livers and spleens of the fetuses. In another experiment, three does in the early weeks of pregnancy were inoculated in the same manner. Four of the offspring of one litter and two of another survived and were studied. Three of the first litter were inoculated intracardially with 1 cc. of a testicular emulsion. The single survivor of this procedure later developed a lesion of the nasal bones. The remaining uninoculated animal was observed for five months without developing any abnormality. One of the offspring of the second litter was also inoculated intracardially and also developed a typical lesion of the nasal bones. Its litter mate was not inoculated but at the age of six months developed a darkfield positive lesion of the nose. Several attempts to repeat this experiment were unsuccessful.

In 1921, Levaditi, Marie and Isaicu (2) mated a normal female to a male rabbit with presumably syphilitic lesions on the glans penis and prepuce. She later developed darkfield positive lesions of the genitalia and gave birth to a litter of young, two of which survived and were successfully inoculated with syphilis at a later date.

The experiences of Brown and Pearce (3), reported in 1925, are of interest. A syphilitic male rabbit was mated with a female which

ten and one-half months before had been inoculated intravenously with an emulsion of a testicular syphiloma. The animal gave birth to a litter of six, one of which was born with a corneal opacity which later disappeared spontaneously. Five of the litter survived for the duration of the experiment. All of them developed peculiar abnormalities of the skin or hair, and all five were later successfully inoculated with syphilis. It was thought that these animals reacted more severely to the infection than normal animals but no controls of the same age were studied. It was also assumed that syphilis was responsible, either directly or indirectly, for the abnormalities of the eye, skin and hair which the animals developed.

In 1926, Fischl (4) reviewed the subject of experimental congenital syphilis and presented his own experiences. He inoculated several pregnant female rabbits intravenously with material from darkfield positive condylomata. The one survivor died shortly after giving birth to a litter of eight young. Two of the litter were born dead and one died shortly after birth. Serial sections of these three animals, stained by the Levaditi method, did not show the presence of treponemes. The five survivors of the litter matured normally for five months. At the end of that time they were successfully inoculated intracorneally with the Nichols strain of *T. pallidum*.

In 1929, Grigoriew (5) successfully inoculated a female rabbit in the anterior chamber of the eye. She was bred several times, but all of her offspring, with the exception of two from a litter born three months after infection, were born dead or died shortly after birth. Both of these survivors developed lesions of the eye. Sections of the cornea of one animal stained with silver showed the presence of treponemes, and in the other infection was proved by the successful inoculation of normal rabbits with its liver and spleen. From this observation, Grigoriew concluded that syphilis was responsible for the non-viability of the offspring of syphilitic female rabbits, and that transmission of infection from the mother to the fetus was possible.

The experiments of Seiffert (6) in 1934 are the most complete of any so far reported. He successfully inoculated three female rabbits with syphilis and bred them a short time later. While normal rabbits inoculated with the liver, spleen, placenta and blood of all three mothers developed syphilis, rabbits inoculated with the fifteen embryos from the three litters were not infected.

PROBLEM

As part of a previous study of syphilis and pregnancy (7) in the rabbit, we found that syphilis was not transmitted from the mother to her offspring, as judged by the failure to infect normal rabbits with an organ emulsion of an appreciable number of such offspring. These results, not yet reported, will be included with the present experiments and considered in detail later. Since our experiences were not altogether in accord with the findings of others, we decided to elaborate our first experiment and to include a study of the development and inoculability with syphilis in the offspring of syphilitic mothers.

Experiments and results

Animals of mixed breeds were used throughout the experiment and the various breeds divided approximately equally among the different experimental groups. All the brood females were inoculated on granulating wounds on the back (8) with the Nichols strain of *T. pallidum*. In every instance infection was proved by darkfield examination of serum expressed from the lesion which developed at the site of inoculation.

Experiment I comprised six females which were bred within four to six days after inoculation. The animals were allowed to go to term and the offspring were sacrificed. The liver, spleen, and hearts were removed from three fetuses from each litter, the organs of the fetuses from each of the six litters were pooled separately, emulsified in a small amount of normal saline, and 1.5 cc. of each of the six emulsions inoculated in both testes of two normal rabbits per emulsion. These animals were observed for 90 days, during which time no lesions of syphilis developed. Eight of them, representing animals originally inoculated with the organs of fetuses from four different litters, were selected for gland transfer. The popliteal nodes of all eight animals were removed; those which had been inoculated with the organ emulsions of the offspring of the same mother were pooled, emulsified in saline and inoculated intratesticularly into normal rabbits. All of these gland transfers were negative. The four inoculated normal males from whom gland transfers were not made were all subsequently (at least 118 days later) successfully inoculated with the Nichols strain of *T. pallidum*.

Experiment II. Five female rabbits were bred within from four to ten days after they had been successfully inoculated and were subjected to hysterectomies a short time before they came to term. Immediately the uterus and its contents were delivered through the abdominal incision, 8 cc. of blood were aspirated from one of the large uterine veins, and 2 cc. injected into each of the testicles of two normal rabbits. Portions of the wall of the uterus were then excised, washed

thoroughly in several beakers of sterile normal saline to free them as thoroughly as possible from blood, emulsified in normal saline and inoculated intratesticularly into two normal rabbits. The placentae were separated from the walls of the uterus and from the fetuses, those from each litter were pooled separately, washed thoroughly in saline, emulsified and inoculated intratesticularly into normal rabbits.

The results of these several inoculations are shown in Table I. Both blood and placentae from all five mothers were infectious for normal males; and infection was produced in two of five instances when the uterus was the inoculum. In the six animals in which uterine inoculation was negative, subsequent lymph-node transfers were also negative.

The entire litters of four of these five mothers were washed thoroughly in sterile saline, the intact fetuses of each litter run separately through a meat

TABLE I

*Results of the inoculation of normal rabbits with the blood, placentae, uteri, and fetuses of syphilitic female rabbits**

RABBIT NUMBER	MATERIAL TRANSFERRED				
	Blood	Placenta	Uterus	Fetuses	
				Number	Result
194	Positive	Positive	Positive	6	Negative
196	Positive	Positive	Positive	4	Negative
210	Positive	Positive	Negative*	13	Negative
281	Positive	Positive	Negative*	Not done	
282	Positive	Positive	Negative*	2	Negative

* Gland transfer of originally inoculated animals also negative.

grinder, and 1.5 cc. of the resultant emulsions of each litter inoculated separately into both testes of two normal rabbits. These animals were observed for 90 days. None of them (see also Table 1) developed any lesions suggestive of syphilis, although several of them developed small testicular abscesses. Repeated darkfield examinations for *T. pallidum* of material aspirated from these lesions were negative. In view of the negative lymph-node transfers in *Experiment I*, gland transfers in this experiment were considered unnecessary. As in *Experiment I*, all of these eight animals were susceptible to inoculation with the Nichols strain of *T. pallidum* at least 118 days after their original unsuccessful inoculation with fetal emulsion.

Experiment III comprised four syphilitic females impregnated immediately after inoculation and allowed to go to term. Their litters totalled 33 offspring, 22 of which survived. Two of the young from two of these four litters were sacrificed, macerated *in toto* in a meat grinder, and 1.5 cc. of the resultant emul-

sions of the offspring of each litter were inoculated separately into both of the testes of two normal rabbits. As in the previous experiments, these inoculations were negative. A compilation of the results of the inoculation of normal rabbits with the viscera of the offspring of syphilitic mothers is shown in Table II.

The 18 survivors of the four mothers of this experiment were divided into three groups as follows:

Group III-A included seven males from three litters. They were inoculated intratesticularly at the age of twelve weeks with a saline emulsion of the pooled popliteal nodes of 3 rabbits with syphilis of 90 or more days' duration. Six developed darkfield positive testicular lesions, and of these one subsequently developed generalized syphilis. The remaining animal developed no local lesion, and lymph-node transfers were negative.

Group III-B comprised five females from three litters inoculated intradermally at the base of the ear at the age of ten weeks with a saline emulsion of a testicular

TABLE II

Results of the inoculation of normal rabbits with organ emulsions of the offspring of twelve female syphilitic rabbits

INOCULUM	NUMBER OF FETUSES	NUMBER OF LITTERS	NUMBER OF ANIMALS INOCULATED	RESULTS			
				Of original inoculation	Of node transfer		
					Number of animals	Number of litters represented	Results
Liver, spleen, heart	18	6	12	Neg.	8	4	Neg.
Entire fetus	29	6	12	Neg.	Not done		
Total.....	47	12	24				

syphiloma containing about three treponemes to each high power dark field. One developed a darkfield positive lesion. Three others developed lesions which were clinically suspicious, but repeated darkfield examinations were negative. Lymph-node transfers from two of these latter animals to normal animals were positive, and from the two remaining animals negative. (See Table III.) One of the three infected animals developed generalized skin lesions.

Group III-C comprised five females and one male from three litters. These animals were not inoculated but were observed for an average of 22 weeks for the development of any defects that might be attributed to the presence of syphilis in the mother. None were observed except that the male animal developed a deformity of both forefeet, with anterior and lateral bowing of the bones of the forelegs at the age of 18 weeks. On the same day this was noticed, a normal rabbit of approximately the same age and with an identical deformity was brought into the laboratory by an animal vendor.

Experiment IV, the control group, included 24 male and female rabbits divided into four groups as follows:

Group IV-A comprised four normal female animals which were bred in the laboratory and their offspring reared there during the course of the experiment. This group was included in order to compare the development of the offspring of syphilitic and non-syphilitic mothers raised in the same environment. One of these mothers aborted at about the third week of pregnancy. The three other animals gave birth to 16 offspring, seven of which survived and were observed for a period of 15 weeks. The litters of the normal mothers were smaller in number and consequently the development of their offspring was more uniform. However, with this exception, no differences in the development of the offspring of syphilitic and non-syphilitic mothers were noted.

TABLE III

Comparison of the results of the inoculation with syphilis of the offspring of normal and syphilitic female rabbits

NUMBER OF RABBITS	SEX	NUMBER OF LITTERS REPRESENTED	INOCULATION		RESULTS INCLUDING GLAND TRANSFER		AVERAGE DURATION OBSERVATION AFTER INOCULATION	NUMBER OF GENERALIZED LESIONS
			Age	Method	Positive	Negative		
Syphilitic mothers								
			weeks				*days*	
12	Male (7)	3	10	Intratesticularly	6	1*	124	1
	Female (5)	3	10	Intradermally	3	2*	130	1
Normal mothers								
12	Male (6)	3	10	Intratesticularly	4	2*	114	0
	Female (6)	3	10	Intradermally	1	5*	103	0

* Lymph-node transfer also negative.

Group IV-B included six female rabbits, the offspring of two normal mothers, inoculated intradermally at the base of the ear at the age of 10 weeks with a saline emulsion of a testicular syphiloma containing three *T. pallida* per high power dark field. This group was included for comparison with the six female animals of the same age which were the offspring of two syphilitic mothers. Only one of this group was successfully inoculated, and this occurred without the development of a lesion at the site of inoculation. Lymph-node transfers from the five remaining animals were negative (Table II).

Group IV-C comprised six male rabbits approximately 12 weeks of age, the offspring of three different normal mothers. They were inoculated intratesticularly with an emulsion of the pooled lymph-nodes of three rabbits with syphilis

of ninety or more days' duration. This group was included for comparison with a group of the same age and sex, but the offspring of syphilitic mothers. Four of the six animals developed darkfield positive lesions at the site of inoculation. Two were refractory to inoculation as proved by negative lymph-node transfer. No generalized lesions were noted during the 114 days the four infected animals were followed.

Group IV-D comprised eight adult male rabbits used as virus controls. All of these developed darkfield positive testicular lesions.

DISCUSSION

In five of the female rabbits in these experiments, treponemes were demonstrated in the blood and placentae; and in two of these, also in the uterus when hysterectomies were performed a few days before the animals were due to litter. Since all the pregnant animals were inoculated in the same manner with the same strain of *T. pallidum* and bred within the same time after infection, it seems reasonable to assume that in the remaining 10 female animals in the experiment treponemes were present in the blood at the time their young were born. It is likewise probable that by the methods used in these experiments it would have been possible to demonstrate treponemes in the placenta and sometimes in the uterus.[1]

This assumption is strengthened by the experiences of Seiffert (6), who also found treponemes in the blood and the placentae of animals infected and bred at approximately the same time. These findings are not unusual, since the infectivity of the organs of animals with syphilis (9) has been demonstrated frequently. However, it is significant that in spite of an infection of the mothers sufficiently extensive to be demonstrable by inoculation of all the organs tested, none of the 47 fetuses from the 12 litters of this experiment harbored an active infection, as judged by the failure to inoculate normal rabbits with an emulsion of their organs. Whether the treponemes were filtered out by or destroyed in the placenta or whether they passed the placenta and were destroyed by the fetus is not apparent. We feel, however, that the results of *Experiment II* support the first of these assumptions, *i.e.*, in the rabbit the placenta forms a barrier to

[1] It should be pointed out, however, that the positive results obtained by inoculating placenta and uterus may possibly have been due to the presence of blood which had not been completely washed out of the tissue.

the passage of the treponemes from the mother to the fetus. Since each of the five mothers in this experiment harbored an active blood stream infection at the time the fetal organs were transferred, the possibility of infection of the fetuses was the same for all five litters. If the treponemes pass through the placenta, one would expect, therefore, unless they were immediately destroyed upon entering the fetal circulation, to find them occasionally in the fetus. This assumption seems particularly applicable to these experiments, since the Nichols strain of *T. pallidum*, which was used in all of them, infects rabbits with great regularity even when the organisms are so few in number that demonstration by darkfield examination is difficult. In addition, comparatively large amounts of the fetal emulsions (1.5 cc. inoculated into each testis of two normal rabbits per emulsion) were used as inocula in an effort to insure a take in case only a few treponemes were present in the fetus. Under these circumstances it is difficult to believe that even a transient invasion of the fetus would always remain completely undetected. If, nevertheless, one assumes that in this experiment invasion of the fetus occurred and that the treponemes were there destroyed, one must also assume, since the average duration of the infection in the mothers at the time the fetal organs were tested was only 33 days, that the immunity of the fetuses to syphilis was much greater than that which the mothers had time to develop (9). It is also evident that if such an immunity exists in the fetus, it entirely disappears by the tenth week of extra-uterine life as evidenced by the susceptibility of the offspring of the syphilitic female rabbits of *Experiment III* to infection at that age.[2]

The experiences of Grigoriew (5) are at variance with these observations. He inoculated female animals intracorneally, and infection in their offspring was demonstrated by silver staining and organ transfer. While this raises the question of a variation in results, depending upon the method of inoculation, it seems more probable that factors outside the experiment, for example, undiscovered disease of the placenta, were responsible for his results. It is improbable, if the placenta acts

[2] It is realized that these experiments do not cover completely the problem of the relationship of fetal syphilis to placental syphilis. Further experiments with this in mind might presumably throw some light on the subject of human congenital syphilis.

as a barrier, that there is a normal variation in its ability to prevent the passage of treponemes from the mother to the fetus.

The experiences of Uhlenhuth and Mulzer (1) are also at variance with our findings and those of other observers. However, their experimental methods are subject to question, since they overwhelmed their animals with infection by the intravenous introduction of large quantities of virus. It is of interest that they were unable to repeat these experiments.

We were unable, also, to detect any difference in susceptibility to infection between the offspring of syphilitic and of normal rabbits. The difference we found between male and female animals, whether the offspring of syphilitic or of normal mothers, was in all probability due more to the different methods of inoculation employed in the two groups than to differences in sex, since both groups were relatively immature when they were inoculated. Moreover, there was no evidence that the offspring of syphilitic mothers reacted more severely to infection than the offspring of normal mothers. This is contrary to the opinion of Brown and Pearce (3), who felt that the course of infection in the offspring of syphilitic mothers was more severe than it was in the offspring of normal animals. That this was an assumption not substantiated by experimental data is evident from their failure to study a group of animals of comparable age which were the offspring of normal mothers.

Fischl (4) also successfully inoculated the offspring of syphilitic mothers. However, since he used a heterologous strain for the inoculation of the offspring, his results are not exactly comparable to our own.

The experiences of Levaditi and his colleagues (2), who infected female animals by mating them with males with darkfield positive genital lesions, are also subject to question. Fischl (4), in a series of experiments, never observed infection of female rabbits as a result of intercourse with a male rabbit with active syphilitic lesions on the genitalia. In addition, Brown and Pearce (10) and Mahoney and Bryant (11) have shown that while infection through the intact mucous membrane of a rabbit is possible, it does not occur without prolonged exposure of these surfaces to *T. pallidum*. One cannot be certain that Levaditi did not confuse the lesions of syphilis with those

of the more easily transmitted infection of spontaneous rabbit spirochetosis caused by *T. cuniculi*.

There is no evidence from our experiments that the presence of syphilis in the mothers influences the growth or development of their offspring. The offspring of non-syphilitic mothers showed the same developmental defects as the offspring of syphilitic mothers, and the mortality for the two groups was approximately the same. This suggests that the peculiarities of development noticed by Brown and Pearce in their animals and the non-viability of the offspring of syphilitic mothers, as noted by Grigoriew, were due to factors outside the experiment and were associated with the problem of rearing animals in the laboratory. As judged by our experiences this is an extremely important consideration, since facilities for the proper breeding of animals are lacking in the average laboratory.

SUMMARY

In a study of 15 female rabbits infected with syphilis and simultaneously allowed to become pregnant, it was found that:

(1) In a group of five animals, treponemes were present in the placentae and blood, and in two of the five, in the uterus.

(2) Transmission of the infection to the fetus did not occur, as judged by the failure to infect normal rabbits with an organ emulsion of 47 fetuses, the offspring of 12 mothers.

(3) Thirteen offspring of four different syphilitic mothers and 12 offspring of five different normal mothers were equally susceptible to inoculation with syphilis.

(4) The course of the infection was no more severe in the offspring of syphilitic mothers than in the offspring of normal mothers.

(5) The developmental defects of seven offspring of three normal mothers born and raised in the laboratory and six uninoculated offspring of three syphilitic mothers were identical and probably were due to the inadequacy of the laboratory facilities for rearing of animals.

CONCLUSIONS

In a study of five pregnant rabbits with early syphilis, treponemes were found in the blood and uteri of the mother and in the placentae. However, no evidence of infection was found in 47 fetuses from 12

different mothers also with early syphilis. It appears that either the placenta forms a barrier to the spread of the infection from the syphilitic female rabbit to her offspring, or the treponemes are destroyed after reaching the fetus. In addition, there was no difference in the susceptibility to infection between the offspring of normal and syphilitic mothers. No difference in the development or viability of the two groups of young was noted that could not be explained by the limitations of the laboratory facilities for the breeding of animals.

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BOOK REVIEWS

Frigidity in Women. By Dr. Eduard Hitschmann and Dr. Edmund Bergler. 76 pp. $2.00. (*Nervous and Mental Disease Publishing Company, Washington and New York, 1936.*)

This brochure is devoted to the psychoanalytic approach toward the problem of frigidity in women. It is a very thorough, careful exposition of the Freudian attitude. In addition to the statement of the philosophical concepts involved, the authors give many illustrations culled from their extensive practices. Even if one is antagonistic to the Freudian doctrine, he will gain much insight into the problem of frigidity by carefully studying this brief book.

The authors decry the current medical attitude of accepting frigidity in woman as the primal curse of her sex. According to them it can be prevented in large part by properly directing the attitude of the child and the adolescent.

A. F. G.

Life Begins. By Morris Braude, Associate Professor of Psychiatry, Rush Medical College. 163 pp. Illus. $2.00. (*Argus Books, Chicago, Ill., 1935.*)

"I have attempted to present the reader with a panorama of the popular ideas, conventions and irregular practices incident to childbirth, from the dim past to the present days" writes the author. And he has succeeded in his purpose almost too well.

The result is a rather confusing but remarkable collection of facts, which are but little correlated. The author shows a wide reading knowledge of world literature and a particularly intimate acquaintance with the Bible and Talmud. In this brief book, he considers the folklore of pregnancy, the foetus, labor, the placenta, the puerperium, lactation and the newborn child. It is to be hoped that in a subsequent book Dr. Braude will select one of these several topics and focus his full attention upon it and thus make a more readable and valuable contribution.

A. F. G.

Gynecology and Obstetrics. (Clio Medica XVII.) By Edwin Jameson. 170 pp. Illus. $2.00. (*Paul B. Hoeber, Inc., New York, 1936.*)

This latest addition to the Clio Medica series has much to recommend it; but the inherent difficulty of crowding the whole history of gynecology and obstetrics into 150 sac-coat-pocket-sized pages makes it a little hard to read. Of necessity, in part it is only a succession of names and dates.

The Early Period deals mainly with the gynecological and obstetrical practices

as revealed by Egyptian Papyri and the Bible. In the chapter devoted to Greece and Rome commendable emphasis is given to Soranus, whom the author quotes liberally. The chapter devoted to the Renaissance stresses the liberalization of anatomic art from its mediaeval shackles and the important influence of the "Rosengarten" and its progeny. In the fourth Chapter, Dr. Jameson summarizes the advances of the seventeenth, eighteenth and nineteenth centuries. Three significant topics—the obstetrical forceps, puerperal fever and gynecological surgery—are chosen from the foregoing for special consideration in separate chapters. This last three-fifths of the book is the most interesting and valuable.

There are several matters of fact and interpretation with which the reviewer takes issue. In his discussion of the Early Period the author considers practices gleaned from early papyri as well as from those of recent and extant primitive peoples. It is still open to question whether a method of treatment used recently among savages has any certain connection with Egypt and Palestine of 3000 years ago. The books of Moses and the Papyrus Ebers were not contemporary, as the author states, but at least 500 years apart; the author of "The Byrth of Mankynde" was not William but Thomas Raynalde; full credit is given to Mauriceau for introducing the bed into obstetrics, whereas, as a matter of fact, Ambroise Paré had recommended it almost a full century earlier in Chapter XVI of his book on the Generation of Man. All the evidence points to Peter Chamberlen the Elder as the inventor of the forceps, not Dr. Peter the son of Peter the Younger, as the book states. The author implies that puerperal sepsis is a disease only of civilization, which would seem to be far from certain. Alexander Gordon is omitted entirely from the Story of Puerperal Fever, an omission which is probably unjustified. The reviewer was considerably puzzled by the italicization of some of the proper names, while others are printed in ordinary type. A typical example follows. "In Germany the operation was performed by *Chrysmar* in 1819 and subsequently by Diffenbach, *Heyfelder*, Kiwisch, *Nussbaum*, Siebold and *Langenbeck*."

A. F. G.

Endocrinology in Modern Practice. By WILLIAM WOLF, M.D., M.S., Ph.D. Pp. 1018. Illus. $10.00. (*W. B. Saunders Company, Philadelphia and New York, 1936.*)

The author has undertaken a colossal job in the writing of this book. Brief descriptions are given of the anatomy and physiology of each of the endocrine glands. Syndromes are described which are thought to be primarily due to dysfunction of these glands, and therapeutic measures are outlined for each syndrome. The author then attempts to outline the effects of diseases in other fields of medicine upon the functioning of the endocrine glands. As regards therapy, it seems to this reviewer that the work is rather sketchy, and in many instances the treatment suggested has little scientific basis for its use. The field which the author attempts to cover is still too much in the evolutionary stage for a work of this scope to be of much practical value to the practitioner, for whom

it is primarily designed. The practising physician would get more help by reference to one or other of the monographs or review articles in the current journals on the subject of his individual case problem. The specialist in endocrinology might find the book useful for purposes of reference, but, in the reviewer's opinion, the absence of a bibliography greatly diminishes its value in this respect.

J. E. H.

Synopsis of Diseases of the Heart and Arteries. By GEORGE R. HERRMANN. 344 pp. Illus. $4.00. (*C. V. Mosby Co., St. Louis, 1936.*)

An attempt to condense the available knowledge in any medical field faces the alternative dangers of incompleteness or the substitution of dogma as a means of bridging the gaps. These Dr Herrmann has largely escaped. He has distilled the essential practical features and scientific facts from the mash of current information concerning Cardiovascular Disease. The result is a small and very useful book containing a critical but unprejudiced synopsis. After describing the methods and instruments of examination, the author discusses all types of cardiovascular disease as regards etiology, anatomical lesion and physiological derangement. His discussion of treatment is founded upon appropriate physiological principles.

In the opinion of the reviewer, exception might be taken to certain of Dr. Herrmann's statements. For example, the "possible nervous mechanism" presented as a cause of essential hypertension might be qualified considerably or included in a discussion of the several theories. Again, the exclusion of arsenical compounds from the treatment of late cardiovascular syphilis is contrary to the practice in this clinic. The cautious administration of neoarsphenamine in controlled cases has yielded undoubtedly beneficial results. Finally, the statement that half of the cases of paroxysmal tachycardia stop abruptly upon "carotid sinus reflex vagus stimulation" seems somewhat of an exaggeration.

The chapter on electrocardiography reflects the author's thorough grasp of this field to which he has already contributed much. From such an authority as Dr. Herrmann the statement on page 89 is particularly welcome:

"There is unfortunately a growing tendency . . . to read far too much into the interpretation of the electrocardiogram. Such men delude themselves by an uncritical attitude which fails to admit the limitations of the method.

"In general, in the absence of pathognomonic signs, regardless of the symptoms the patient may present (with the possible exception of typical angina pectoris), slight slurring or notching in the electrocardiogram does not warrant the diagnosis of heart disease."

E. C. A.

Neurological Surgery. By LOYAL DAVIS. 429 pp. Illus. $6.00. (*Lea and Febiger, Philadelphia, Pa., 1936.*)

This volume does not, as its title might suggest, deal with the whole field of neurological surgery, but it does accomplish very satisfactorily the task set forth in the preface. In other words, it provides the practising physician with enough

facts to enable him to give his patients advice concerning the possibilities of neurological surgery. Furthermore, the scope of the book need not be limited to practising physicians, because medical students and house-officers can benefit by reading it and can find enough ammunition in its pages to blow up the arbitrary practices of many who specialize in neurosurgery. The subject matter in the respective chapters is well apportioned, nicely balanced, and well illustrated by cases from the extensive experience of the author. No volume of this size can be expected to be wholly complete, yet one misses references to such subjects as third ventriculostomy, neurinomas of peripheral nerves, and meralgia paraesthetica. The author has minimized quite justly references to operative technique; but if technique must be described, as was done for the operation of section of the sensory root of the fifth cranial nerve, then why not mention a simple matter which has probably saved the life of many patients and which has received scant attention in the medical literature, namely, the prompt release of air from the lateral ventricles after an air injection for a ventriculogram? A particularly praiseworthy feature is the sound judgment and conservatism which is apparent in every chapter, and in none more deservedly so than in the one on the surgery of the autonomic nervous system. Another valuable part of the book is the good selection of references, which are well chosen and often very recent. In brief, this book can be consulted with profit by any one who has a patient suffering from a neurosurgical lesion.

F. C. L.

A Text-Book of Histology. By J. LEWIS BREMER. 5th ed. 580 pp. Illus. $6.50. (*P. Blakiston's Son & Co., Philadelphia, 1936.*)

This text-book, as the title page asserts, is arranged upon an embryological basis. The discussion of each organ is preceded by a carefully written consideration of its growth and development as well as a short historical sketch indicating the names of early workers together with the meaning of the terms used. The bibliography contains some 500 titles, nicely distributed between the older classical work and recent contributions, so that any serious student could use the text-book as a point of departure for reading more thoroughly on any subject found in histology except perhaps that which might be designated as functional cytology. The book as a whole gives an excellent account of the minute morphology of the organs of the body. It has many new illustrations, quite a task to achieve for a text-book which is now in its fifth edition.

Several unusual features stand out. The nomenclature used for blood is that which has been generally accepted for years—a distinct relief. Also, the author has the happy faculty of treating his subject without bias. The lack of emphasis upon the lines and "membranes" in skeletal muscle is timely, and there is an unusually good description of the teeth and gums. The new work on the lung has been incorporated. The special organs of sensation are well described.

The classification of the various tissues of the body and the types of glands offer nothing fundamentally new. No attention has been paid to that rather discon-

certing subject of mucous-like glands, which secrete no chemically identifiable mucus, and to serous-like glands, which secrete no enzymes. In fact, the treatment of the externally secreting glands is not on a par with that given the internal secreting glands or, for that matter, with that given the liver and the kidney. Moreover, the reviewer was glad to note that the capacity for differential regeneration of the fundamental tissues was considered.

The student will find in this text-book simple straightforward descriptions of the morphology of the organs of the body, which together with that of their embryology will give him an excellent orientation in knowing their structural arrangements. If, however, he were interested in the physiological activities of cells within organs, he would have to look elsewhere. But the reviewer knows of no single book in which organogeny is as nicely related to microscopic structure as Bremer has shown it to be in this new text-book of histology. And that is what he attempted to do.

M. H.

Why Bring That Up? A Guide To and From Seasickness. By DR. J. F. MONTAGUE. 131 pp. Illus. $2.00. (*The Home Health Library, New York, 1936.*)

This is an amusing little essay originating from the belief that curing seasickness has always been, and will forever be, a strictly amateur sport. It may serve as a bracing prophylactic for those who anticipate the dreaded *mal de mer*. Detailed directions are given for conservative treatment.

J. B., III

Oxford Medicine. Vol. vii. Psychiatry for Practitioners. By various authors. Edited by Henry A. Christian. 634 pp. $10.00. (*Oxford University Press, New York, 1936.*)

In his preface the editor expresses his conviction that the major interest of the general practitioner and of the psychiatrist in the patient, as a living being, has reached the point where the artificial barriers, which tradition had erected between the two disciplines, are publicly declared no longer to exist.

This volume, which purports to give a survey of the psychiatric field for general practitioners, is a most welcome contribution to recent psychiatric literature. The list of contributors is notable: Bond, Cheney, Ebaugh, Henderson, Kahn, Palmer, Pearson, Ross, Strecker, White, Whitney.

The handling of the material is highly commendable with, on the whole, an admirable minimum of debatable hypothesizing but at the same time without becoming ultra-dogmatic. On the whole, the book constitutes an excellent presentation of American psychobiologic psychiatry and bears clear imprint of, and gives credit to, the teachings of Adolf Meyer. Only one chapter, that on "The Psychiatry of Childhood" by Gerald Pearson, has a strong psychoanalytic systematization. This chapter appears as a stranger among the others, and its insistence on the psychoanalytic viewpoint would seem to be not only out of

keeping with the rest of the book but also with its main purpose, in its appeal to general practitioners.

Although the book is dedicated to practitioners, it could easily qualify as a reference text for psychiatrists. In fact, this reviewer feels that it would be only a rare general practitioner who would have the time and the interest to utilize all the material here presented. The book can be recommended and the editor complimented on the inclusion of such a work in the loose-leaf system of medicine.

W. M.

Chemical Procedures for Clinical Laboratories. By MARJORIE R. MATTICE. 520 pp. Illus. $6.50. (*Lea and Febiger, Philadelphia, 1936.*)

The author of "Chemical Procedures for Clinical Laboratories" is Assistant Professor of Clinical Pathology at the New York Post-graduate Medical School of Columbia University and Assistant Director of the Biochemical Laboratory of the New York Post-graduate Hospital. This volume promises to be valuable for a number of reasons, not the least of which are its simplicity, excellent organization and lucidity of expression.

As the title implies, this work is intended primarily as a guide to persons using chemical methods in clinical laboratories, but it should be helpful also to a large group of students and investigators who want simple, explicit, up-to-date direction in this complicated field. It is not intended to serve as an exhaustive treatise on biochemical methods. It is divided into four parts devoted to "The Blood," "The Urine," "Gastro-intestinal Secretions" and "Miscellaneous Biological Fluids," and in addition it contains an appendix in which there has been collected a wealth of useful information on such subjects as preparation of reagents, calculation of results and errors, etc.

In presenting these technical procedures the author has used discrimination in giving instructions useful to the inexperienced, which all too often are taken for granted. She has included, simply and briefly, enough theoretical discussion to provide a purposeful background to the analyst, and sufficient consideration of normal and pathological findings to orient him in the interpretation of results.

M. V. B.

The Patient and the Weather. By WILLIAM F. PETERSEN, M.D. With the assistance of Margaret E. Milliken, S. M. Vol. I, Part 2. Autonomic Integration. 781 pp. Illus. $9.00. (*Edwards Brothers, Inc., Ann Arbor, Mich.*)

In Part 1, previously published with the subtitle "Footprint of Asclepius," the author discussed the distribution of diseases in the United States in relation to meteorological conditions. In Part 2, after an interesting introductory discussion of constitution and an exposition of its importance or probable importance as a significant factor in functional as well as in chronic infectious diseases, the book goes on to a very detailed consideration of what the author designates as autonomic integrations, or the reactions of the meteorological environment on the autonomic mechanisms of the body. There is first a general presentation of the

physics of the air and its movements and of the historical aspects of meteoropathology, and then an analysis of the study of four normal young men, "representing different physical habitus as well as different psychic and mental reactivity," for a period of two months during the summer of 1932. The data are presented in great detail with many tables and graphs. On the basis of these findings a differential study is made by the same methods of two men of different habitus, one a normal pyknic and the other a normal leptosome. Special chapters are devoted also to the effect of the environment on the bacterial flora, upon the male as compared with the female, upon children, etc. Something of a summary is given in the final chapter under the striking title "The Human Organism as a Cosmic Resonator." His general conclusion is summed up in the statement that "a biological rhythm or tide is initiated by the atmospheric circulation. The two poles of this continuous organic rhythm I have designated as the ARS and COD phases." The ARS phase is characterized by a number of physiological reactions, but in general it indicates a state of "relative tissue quiescence," while the COD phase is one of "general metabolic stimulation."

In the preface to this part, as also in the preface to Part I, the author makes an eloquent and convincing plea for the necessity of a study of environmental and especially meteorological factors in relation to diseases. Dr. Petersen deserves much credit for his insistence upon this point and for all the labor that he has expended in his efforts to establish it upon a scientific basis. One readily admits with him that the subject has been neglected and that intensive scientific work in this field is greatly to be desired, but the reviewer feels that it would have been more helpful, possibly, to the purpose in view if the data collected with so much trouble had been analyzed in a somewhat more critical spirit.

W. H. H.

Food, Fitness and Figure. By JACOB BUCKSTEIN. 252 pp. $2.00. (*Emerson Books, Inc., New York, 1936.*)

"Food Fitness and Figure," a general survey of the field of nutrition, is written in a simple but accurate manner. Its complete lack of medical terms makes it an excellent text for the layman.

After reviewing briefly the early history of foods, the author brings us down to the present era by discussing individually proteins, fats, carbohydrates, minerals and vitamins.

He then discusses some of the common specific foods, such as dairy products, bread, vegetables, meat and beverages, and their place in the normal diet.

Several chapters are devoted to food fads and fancies. The attack is centered chiefly around the fallacies of the vegetarianism theory, the Hay diet, fasting and various reducing agents which are known to have a harmful effect upon the body.

The problem of weight control is discussed in some detail. This is supplemented by charts of a 14-day diet to lose weight, a 14-day diet to maintain weight, a 14-day diet to gain weight, tables of 100-calorie portions of the more common foods, and standard weight charts.

E. R. T.

Principles and Foibles of Cancer Research. By WILLIAM RIENHOFF, SR., M.D., F.A.C.S. 200 pp. unbound, $2.50. (*Waverly Press, Inc., Baltimore, 1936.*)

This book, written about the fixed idea that cancer is due to the invasion of a living virus into cells of which the cell membrane has been rendered permeable by some injury, discusses in great detail an immense mass of literature dealing especially with that trend of the investigation. All other possible causes, such as chemical or physical carcinogenic agencies, are regarded as producing the injuries which make the cells permeable to this agent. No distinction is made among tumors except to separate cancer from sarcoma, and other tumors are not considered. It is confidently felt that before long, with attention directed along this line, the nature of cancer will be as clearly understood as that of tuberculosis.

The book reveals a great concentration upon the study of this subject and there are more than six hundred references to the literature. It covers a long period from the earliest to the most recent writings, and since the main idea is plausible, it forms a valuable storehouse of information. Complications of the language make it difficult to read, but the summary of the contents is clear.

W. G. M.

A Text-Book of Pathology. By W. G. MACCALLUM. 6th Ed. Entirely reset. 1277 pp. Illus. $10.00. (*W. B. Saunders Co., Philadelphia, 1936.*)

The present edition of MacCallum's Pathology marks the twentieth anniversary of this justly famed text. The first edition was immediately welcomed everywhere by pathologists, students and physicians with an enthusiastic appreciation that very few text-books either merit or receive. It was written with lucidity and great charm, and with an inquiring, critical attitude made sound by a rich personal experience with the subject matter; it was refreshingly free from the stuffy dogmatism and fossilized concepts that abound in the ordinary text-book; and, for the first time, pathology was treated systematically from the standpoint of etiology. Dr. MacCallum viewed each disease as an entity composed of the effects of an injury and the body's reaction to that injury, and he accordingly discussed systematically the effects of each form of injury, each cause of disease, upon the entire body, instead of following the universal and highly artificial method of taking up for discussion one isolated organ after another and cataloguing all of the heterogeneous and unrelated injuries that can possibly affect each separate organ. In MacCallum's book one could read the coherent story of a given *disease*, or of all of the different disease entities that a given injurious agent or condition is capable of producing. In other text-books one could read in continuity only about a given *organ*, *i.e.*, all of the possible ills that might befall that organ without reference to the rest of the body—in each case a conglomeration of injuries as unrelated among themselves as "shoes and ships and sealing wax and cabbages and kings." Of course, in the present incomplete state of knowledge it is impossible to write of all diseases from a strictly etiological standpoint, and compromises had necessarily to be made; but Dr. MacCallum's attempt was a fundamentally important move in the right direction, and the extraordinary

success of the book during the past twenty years attests plainly enough the appreciation which his method of treatment aroused.

In the beginning, as the preface to the first edition tells us, the book was planned primarily to set forth the fundamental principles of Pathology rather than to serve as a complete reference work. In each succeeding edition, however, more and more individual diseases were added. It is now a pleasure to find that the subject matter of this last edition (the sixth) has been so greatly enlarged that the volume serves equally as a critical analysis of the fundamental principles of disease and as a reference book in which all important disease conditions are described and discussed. In addition, every former chapter has been thoroughly worked over in the light of recent advances in knowledge, many new and excellent illustrations have been added, and the whole has been entirely reset by the publisher, with the result that the great increase in subject matter is accommodated with little increase in the size of the volume and no decrease in the size of the type.

From the standpoints of soundness of critical judgement, accuracy of detail, stimulating presentation and excellence of literary style the present volume, in the opinion of the reviewer, is easily the best text-book of pathology available in any language today.

BOOKS RECEIVED

A Text-Book of Pathology. By W. G. MacCallum. 6th ed., entirely reset. 1277 pp. Illus. $10.00. W. B. Saunders Co., Philadelphia, 1936.

Gynecology and Obstetrics. By Edwin Jameson. [Clio Medica, xvii]. 170 pp. Illus. $2.00. Paul B. Hoeber, Inc., New York, 1936.

An Introduction to Psychological Medicine. By R. G. Gordon, N. G. Harris and J. R. Rees. 386 pp. $4.00. Oxford University Press, London, 1936.

A Text-Book of Histology. By J. Lewis Bremer. 5th ed. 580 pp. Illus. $6.50. P. Blakiston's Son & Co., Philadelphia, 1936.

Chemical Procedures for Clinical Laboratories. By Marjorie R. Mattice. 520 pp. Illus. $6.50. Lea & Febiger, Philadelphia, 1936.

Tissue Immunity. By Reuben L. Kahn. 707 pp. Illus. $7.50. Charles C. Thomas, Springfield, Ill., 1936.

A Text-Book of Physiology. By William H. Howell. 13th ed., thoroughly revised. 1150 pp. Illus. $7.00. W. B. Saunders Co., Philadelphia, 1936.

A Manual of Pharmacology. By Torald Sollmann. 5th ed. Entirely reset. 1190 pp. $7.50. W. B. Saunders Co., Philadelphia, 1936.

Starling's Principles of Human Physiology. 7th ed. Edited and revised by C. Lovatt Evans and H. Hartridge. 1096 pp. Illus. $8.75. Lea & Febiger, Philadelphia, 1936.

Encyclopedia of Sexual Knowledge. By A. Costler and A. Willy and others, under the general editorship of Norman Haire. 567 pp. Regular price $6.00. Popular priced edition $3.00. Eugenics Publishing Co., New York, 1934.